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Review Article

Systemic Lupus Erythematosus and Antiphospholipid Syndrome

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Abstract

Antiphospholipid syndrome is an autoimmune disorder defined as association of vascular thrombosis and/or pregnancy complications with presence of antiphospholipid antibodies (lupus anticoagulant, anticardiolipin and anti-β2 glycoprotein I). It is the most common cause of acquired thrombophilia, and can occur as an independent entity or in relation with other diseases, especially systemic lupus erythematosus. Presence of antiphospholipid syndrome in systemic lupus erythematosus is additional vaso occlusive factor in already present inflammation, bringing further risk for thrombotic events. Clinical and serological manifestations of antiphospholipid syndrome and systemic lupus erythematosus are very similar, so possible connection for these two autoimmune disorders is assumed.

Introduction

Antiphospholipid syndrome (APS) is an autoimmune disorder defined as association of vascular thrombosis and/or pregnancy complications with presence of antiphospholipid antibodies (lupus anticoagulant, anticardiolipin and anti-β_2 glycoprotein I). According to revised criteria, at least one clinical and one laboratory criteria are necessary for diagnosis (Table 1) [1]. The spectrum of clinical manifestations of APS is broad, because thrombosis can occur in both arterial and venous system and in the blood vessels of all sizes. Confirmation of antiphospholipid antibodies is very important step for diagnosis, but because they are polyclonal and heterogeneous, it is difficult to make a standardized test which includes them all.

Antiphospholipid syndrome can occur as an independent entity and then is called primary. Secondary APS is most commonly seen in autoimmune diseases, but also in malignancies, hematological, infectious and neurological diseases. A special form is catastrophic APS, characterized by acute multiorgan failure caused by rapid microthrombosis [2].

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by autoantibodies formation and organ changes caused by inflammation and other blood vessel disorders. Beside familiar risk factors for thrombosis in patients with SLE, antiphospholipid antibodies are among most significant. Since positive lupus anticoagulant (LA) and/or anticardiolipin (aCL) antibodies are one of classificaton criteria for SLE, patients are regularly tested for their presence and their confirmation is additional risk factor for thrombosis [1, 3, 4].

Patients with primary APS can have clinical and serological manifestations as in SLE, but not fulfilling criteria for diagnosis of SLE [5,6]. Some of them over the years can develop SLE. Secondary APS is most commonly associated with SLE. These findings may suggest that there is possible overlaping between these two disorders.

Table 1: Classification criteria for Antiphosholipid syndrome.

Clinical criteria
1. Vascular thrombosis One or more clinical episodes of arterial, venous, or small vessel thrombosis, in any tissue or organ. Thrombosis must be confirmed by objective validated criteria
2. Pregnancy morbidity a. One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, *or* b. One or more premature births of a morphologically normal neonate before the 34th week of gestation because of: (i) eclampsia or severe preeclampsia defined according to standard definitions, or (ii) recognized features of placental insufficiency, *or* c. Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.
Laboratory criteria
1. Lupus anticoagulant (LA) present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis
2. Anticardiolipin (aCL) antibody of IgG and/or IgM isotype in serum or plasma, present in medium or high titer (i.e. >40 GPL or MPL, or >the 99th percentile), on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA (*Enzyme-linked immunosorbent assay)*
3. Anti-β2 glycoprotein I antibody of IgG and/or IgM isotype in serum or plasma (in titer >the 99th percentile), present on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA, according to recommended procedures

Pathogenesis of antiphospholipid syndrome

Pathogenesis of APS is complex. Antiphospholipid antibodies are very heterogeneous, and though their name implies, they are not directed against phospholipids as such, but against phospholipid-binding proteins. The main autoantigen for antiphosholipid antibodies is β-2 glycoprotein I, plasma protein composed of five domains. Upon binding to an anionic phosholipid surface through domain V, the cryptic epitope on the domain I becomes exposed, alowing antiboides to bind [7-9]. This antigene-antibody complex interact with receptors of different cells (endothelial, thrombocytes, monocytes) and activate them, causing increased tissue factor expression, cytokine and adhesion molecule release, therefore achieving prothrombotic potential [9-11].

Although APS is considered to be non inflammatory disorder, researches on animal models have found that complement activation and inflammation rather than thrombosis are essential in fetal loss [12]. The role of β-glycoprotein I as a regulator protein of the complement system has been postulated, so the presence of antiphosholipid antibodies may inhibit this function, leading to complement activation and consequential neutrophil attraction, activation of neutrophils and monocytes and the release of inflammatory mediators [11, 14]. These findings are connected with the pathogenesis of SLE and can have therapeutic implication, such as therapy with humanized monoclonal antibody against complement protein C5 [13].

Patients with APS have occasional, mostly localized thrombotic events and rarely present with disseminated thrombosis despite continuously present antiphospholid antibodies. Since anion phospholipids are usually not exposed to circulation, it is assumed that occurrence of thrombosis requires "two hits". First hit is presence of antiphospholipid antibodies with procoagulant and proinflammatory potential and second one is stimulation of vascular structures and cells with cytokines, injury or local apoptosis, exposing anion phospholipids to antiphospholipid antibodies [8]. In the context of SLE, already present injury of the vascular structures and inflammation may enhance the thrombotic potential of antiphospholipid antibodies leading to thrombosis.

Prevalence of antiphospholipid syndrome in systemic lupus erythematosus

Prevalence of APS in SLE is 20-50%, and antiphospholipid antibodies occur in 5-70% of SLE patients [15,16]. Large European cohort study of 1000 APS patients from 13 countries demonstrated that primary APS was present in 53.1% of patients, and APS was associated with SLE in 36.2%, 80% of which had aCL antibodies, 20% had LA, and about 60% had both [17]. Prevalence of anti- β_2 glycoprotein I (GPI) antibodies in patients with SLE without thrombosis is 7.8-34.9%, and in those with SLE and secondary APS is 35% [18]. Thrombosis is more frequent in patients with SLE and antiphospholipid antibodies compared to those with some other autoimmune disease and these antibodies [19]. Thrombosis in SLE is also associated with anti-β_2 GPI antibodies of IgA isotype, which are not included in criteria for diagnosis of APS [20, 21]. Determination of these antibodies is recommended in case of clinical symptoms of SLE and/or APS, particularly if other tests for antiphospholipid antibodies are negative [22].

Clinical manifestations

Among diverse clinical and laboratory manifestations of APS there are also those not included in classification criteria: heart valve changes, livedo reticularis, skin ulcerations, thrombocytopenia, nephropathy, cognitive dysfunction, migraine, epilepsy, aCL antibodies of IgA isotype, anti- β_2 GPI antibodies of IgA isotype, anti-phosphatidylserin (aPS)

antibodies, anti-phosphatidiletanolamin (aPE) antibodies, anti-thrombin antibodies (aPT), antibodies to complex phosphatidylserin-prothrombin (aPS/PT), anti-anexin 5 antibodies [23-28]. Including these manifestations in classification criteria would decrease diagnostic specificity for APS, but the question remains when they should be considered in diagnosis establishment [1].

As well as in patients with primary APS, clinical manifestations are diverse in patients with SLE and secondary APS with most common being lower extremities deep venus thrombosis (DVT), cerebrovascular insult and transitory ischemic attack, but some less frequent also occur, like myocardial infarction, avascular bone necrosis and spleen infarction [17, 29]. Interesting topic regards thrombocytopenia and APS nephropathy as non classification manifestations of APS in patients with SEL.

Thrombocytopenia is common in patients with SLE and secondary APS and more common than in those with primary APS [1, 30]. It is mostly mild with manifestations varying from bleeding to thrombosis. It is questionable when to regard thrombocytopenia in the presence of antiphopholipid antibodies as clinical non classification criteria for secondary APS and when as a diagnostic criteria for SLE. This is important issue, because it has therapeutic implications.

Antiphosholipid syndrome nephropathy clinically manifests with arterial hypertension, low grade proteinuria and acute or chronic kidney failure. Study of Tektonidou et al. demonstrated that APS nephropathy occurs in 39.5% of patients with SLE and antiphospholipid antibodies, and in only 4.3% of those with SLE without antiphospholipid antibodies [31]. Nephropathy was confirmed by pathohistological analysis of kidney biopsies and was statistically strongly correlated to positive LA, aCL antibodies, livedo reticularis and arterial thrombosis. The authors concluded that APS nephropathy in patients with SLE represents an independent risk factor for arterial hypertension and serum creatinine levels, influencing poorer prognosis of kidney function. These results are significant for demonstration that pathohistological analysis of kidney biopsy is required for differentiation of patients with APS nephropathy from those with lupus nephritis. Pathology report affects treatment strategy, namely application of intensive immunosuppressive therapy. On the other hand, patients with SLE can have both lupus nephritis and APS nephropathy, which leads to worse prognosis of kidney function.

Thromobosis risk in patients with systemic lupus erythematosus

Longitudinal studies have confirmed that APS can develop in 50-70% of patients with SLE and antiphospholipid antibodies during 20 years of follow up [19]. Since patients with SLE can have antiphospholipid antibodies, it would be important to identify clinical and laboratory parameters predictive of future thrombosis.

According to study results of Tarr et al. who followed 272 patients with SLE over 5 years, LA was most frequently associated with thrombotic events, namely neurological manifestations and lower extremities DVT [32]. Patients with long standing positivity of different antiphospholipid antibodies had the highest risk for thrombosis. A half of patients with SLE with antiphospholipid antibodies had thrombotic complications. When it comes to clinical manifestations of SLE, lupus nephritis and Raynaud phenomenon are verified as risk factors for thrombotic events in patients with antiphospholipid antibodies [33].

In a study that retrospectively analyzed profile of 6 different antiphospholipid antibodies (LA, anti- β_2 GPI, aCL, aPE, aPT, aPS/PT) in 230 patients with SLE, a combination of LA, anti- β_2 GPI and aPS/PT antibodies had the highest specificity for APS and was associated with higher risk for thrombosis and pregnancy complications compared to triple positivity of LA, anti- β_2 GPI and aCL antibodies [34].

A recent cross sectional study of 211 patients with SLE analyzed independent thrombotic risk factors, conventional cardiovascular risk factors, antiphospholipid antibodies profile including non classification antiphospholipid antibodies and a profile of other antibodies. Arterial hypertension, hyperlipidemia, aCL, LA, anti-β_2 GPI and aPS/PT antibodies were designated as independent risk factors for thrombosis and fetal loss during pregnancy [35].

Primary antiphospholipid syndrome and systemic lupus erythematosus

It is a well known paradigm that patients with certain autoimmune disorder should be regularly evaluated for development of other autoimmune disease. Patients with SLE are followed for potential development of secondary APS. Still, there are few available studies that dealt with opposite question - whether patients with primary APS can develop SLE as well.

Study analyzing 128 patients with primary APS demonstrated that 8.2% of them also developed SLE during 8 years of follow up [36]. Authors verified increased risk for SLE in patients with positive family history for SLE, Raynaud phenomenon, migraine, psychiatric disorders, haemolytic anemia, low C3 and C4 levels and positive Coombs test. Only positive Coombs test reached statistical significance as a risk factor for SLE and was designated as a potential

marker for SLE development. Retrospective study of Tarr et al. which analyzed 362 patients with SLE, demonstrated that primary APS was previously present in 7.2% of patients, and that patients with primary APS develop SLE on average after 5.5 years. [37]. McClain et al. analyzed significance of appearance of positive aCL antibodies before SLE development, and confirmed that patients with positive aCL antibodies fulfilled SLE criteria approximately over 3 years. Clinical disease course in these patients was more difficult and positive aCL antibodies were significantly correlated with kidney lesions, neurological complications, thrombocytopenia and thrombosis [38]. Hungarian authors, who retrospectively analyzed 165 patients with primary APS, found that 63% of them still had primary APS after 5 years, that 14.4% developed undetermined systemic connective tissue disease and that 23% developed specific autoimmune disease (most often SLE, 8% of patients) [39]. Authors didn't verify any possible laboratory prognostic marker for development of some of the systemic connective tissue diseases during transitional period from primary APS to definitive diagnosis of other autoimmune disease.

Based on these findings, it can be concluded that patients with primary APS should be regularly followed for development of SLE. Some authors believe that primary APS is just an early phase in a dynamic process of transition to a defined autoimmune systemic disease [32,37].

Therapy

Main therapeutic goal in patients with APS is a prevention of new thrombosis. There are no official guidelines and recommendations are mostly based on systematic reviews of published results of mainly observational studies. Clinical difference exists between patients with positive antiphospholipid antibodies without manifested APS and those with established APS. Treatment of APS in pregnancy is a separate issue. Therapeutic approach varies depending on clinical situation, so primary and secondary thromboprophylaxis can be discussed.

Most studies dealing with primary thromboprophylaxis examined acetylsalycilic acid. Prospective double blind placebo controlled study that compared use of Aspirin (81 mg daily) to placebo in asymptomatic patients with positive antiphospholipid antibodies, didn't confirm prophylactic effect of Aspirin on development of thrombosis [40]. Still, thromboprophylactic effect of Aspirin was demonstrated in patients with SLE compared to those without therapy [41]. After systematic literature review Tuthill et al. recommend use of low dose Aspirin in patients with persistently positive antiphospholipid antibodies (especially LA), with addition of hydroxychloroquine if SLE is also present [42]. Authors advise mandatory estimation of other thrombotic risk factors, their active reduction and treatment. In situations of increased risk for thrombosis, prophylactic use of low molecular weight heparin is advised. Antimalarics have anti-inflammatory, immunomodulatory and metabolic effects, so hydroxychloroquine is recommended for all patients with SLE and positive antiphospholipid antibodies [43, 44].

Patients with APS are at increased risk for recurrent thrombosis which makes issue of secondary prophylaxis very important. Therapeutic approach is based on anticoagulant therapy, but treatment goals are different depending on whether arterial or venous thrombosis happened. Based on recommendations from different authors, therapy of patients with APS and first episode of venous thrombosis consists of long term use of oral anticoagulants , with therapeutic range of INR (*international normalized ratio*) of 2-3 [42, 45, 46]. Differences exist in recommendations for optimal INR therapeutic range in patients with first episode of arterial thrombosis or recurrent thrombosis. Some authors advise only oral anticoagulants with INR range of 3-4, while others recommend INR range of 2-3, or use of oral anticoagulants (INR 2-3) and antiaggregation therapy [46, 47]. Large prospective studies are required for unified recommendation. Meanwhile therapy should be individualized, with respect to all potential thrombotic risk factors, but also potential bleeding risk factors. Modern therapeutic modalities have been debated during last 14th International Congress on Antiphospholipid Antibodies, namely direct oral thrombin inhibitors, inhibitors of factor Xa, statins, B cell inhibitors, inhibitors of complement components and peptide therapy [44].

Is antiphospholipid syndrome a systemic autoimmune disorder?

Patients with primary APS and those with SLE (without APS) have similarities that are serological (LA, aCL) and clinical (livedo reticularis, neurological and nephrological manifestations, thrombocytopenia) [48]. Many patients with primary APS have serological markers of SLE (antinuclear, anti ds-DNA, anti-nucleosomal antibodies), and then they are said to have a "lupus like disease". Some of them can develop SLE over years. On the other hand, prevalence of secondary APS is highest in patients with SLE, so it can be assumed that SLE represents an inflammatory basis for APS. Additionally, experimental models suggest significant role of complement system and inflammation in APS pathogenesis, which is similar to SLE pathogenesis [49-51]. New data indicate role of vitamin D in SLE pathogenesis and also very current are researches of vitamin D role in APS [52]. Based on many similarities with SLE, some authors indicate possible systemic character of APS and raise an intriguing question: are

APS and SLE two separate autoimmune disorders or represent one same autoimmune phenomenon? [53, 54].

Conclusion

Antiphospholipid syndrome is autoimmune disorder with complex pathophysiological mechanisms, diverse clinical and laboratory manifestations and insufficiently defined therapy recommendations. Knowing that certain manifestations are not included in classification criteria, it is clear that official criteria simply don't apply to some patients. Still, it is questionable which situations require strict following of classification criteria and which don't. That is why patients should be regarded individually, with respect to all thrombotic risk factors, clinical picture and availability of tests for antiphospholipid antibodies, but also to risks of possible complications of antithrombotic therapy.

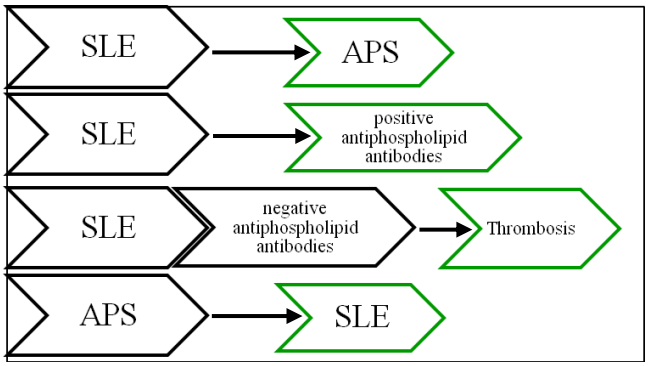

Figure 1: Possible clinical forms in evolution of SLE and APS. (SLE- systemic lupus erythematosus, APS- antiphospholipid syndrome).

Patients with SLE can develop APS during disease course. Among all autoimmune diseases, secondary APS is most commonly seen in patients with SLE. On the other hand, patients with SLE can have antiphospholipid antibodies, but without clinical manifestations of APS. Also, patients with APS can develop SLE over years. All these clinical scenarios indicate that patients with SLE should be carefully observed for development of APS, but also vice versa, patients with APS should be monitored for development of other autoimmune disease, especially SLE (Figure 1).

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