1. Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune and inflammatory disease. There are many tissues and organs involved in the course of the disease: skin, joints, kidneys, serous membranes, and haematopoetic, nervous and cardiovascular systems as well. The course of the disease is characterized by periods of exacerbations and remissions (Bombardier et al., 1992).

The crucial role in SLE pathogenesis plays dysregulation of both the innate and adaptive immune systems. Defective function of T cells and overactivation of B cells as well as defective clearance of apoptotic debris cause the production of autoantibodies, formation and deposition of immune complexes and, consequently, systemic tissue and organ damage (Shoenfeld et al., 1999; Muñoz et al., 2010).

On the other hand, an involvement of both innate and adaptive immunity in atherosclerosis pathogenesis is well documented and recent data clearly characterize atherosclerosis as an inflammatory and autoimmune disease. The presence of monocytes/macrophages transformed into lipid loaded foam cells, natural killer cells, dendritic cells, mast cells and immunoglobulins within the plaque has been documented. Various autoantibodies have been reported to associate with atherosclerosis including anti-heat shock protein 60/65, anti-oxidized low density lipoprotein (aoxLDL) and selected antiphospholipid antibodies (aPL) (George et al., 2000; Gordon et al., 2001; Doria et al., 2005).

There is also a growing bulk of evidence on the strength of association between systemic connective tissue diseases, such SLE and premature and accelerated atherosclerosis development (Fischer, 2008; Doria et al., 2003) and atherosclerotic cardiovascular events are considered a leading cause of mortality in those patients (Borchers, 2004). Because traditional risk factors alone fail to fully account for accelerated atherosclerosis in SLE (Esdaille et al., 2001; Lee et al., 2010), it has been attributed to complex interactions between traditional risk factors and factors associated with the disease process and its treatment (Svenungsson et al., 2001; Bruce et al., 2000).
The purpose of this chapter was to review the risk of atherosclerotic disorders development in SLE as well as antiphospholipid syndrome (APS) patients, and to analyze the role of selected immune mechanisms in atherosclerosis pathogenesis, including potential role of autoantibodies, especially aPL.

2. Atherosclerosis in systemic lupus erythematosus – The background

Initial reports on the development of early atherosclerotic lesions in patients with SLE came from autopsy examinations performed by Bulkley and Roberts in 1975 (Bulkley & Roberts, 1975). A year later, these observations were confirmed by other investigators, who developed a bimodal pattern of causes of mortality in this patient group, indicating that the first mortality peak applies to patients with active SLE, concurrent renal involvement, and recurrent infections, who were treated with high dose glucocorticosteroids. The second mortality peak was observed in patients with inactive SLE, who had been treated with glucocorticosteroids for many years and had previous myocardial infarction (Urowitz et al., 1976).

Study performed at the University of Pittsburgh Medical Centre from 1980 to 1993 showed that women with SLE in the 35- to 44-year age group were more than 50 times more likely to have myocardial infarction than women of similar age in the Framingham offspring cohort. Overall, risk of myocardial infarction in SLE female patients was 6-fold higher in comparison with the general population. Of note, two thirds of all first cardiac events occurred in women younger than 55 years old (Manzi et al., 1997). Similar data demonstrated cohort study at Toronto lupus clinic. The rate of myocardial infarction in lupus patients was 5 per 1000 persons in comparison with 1 per 1000 persons in the general population from 1993 to 1994 and the mean age of first cardiac episode was 49 years in SLE patients compared with the peak incidence in the general population aged 65 to 74 years (Bruce et al., 2000).

Furthermore, the report from the Toronto SLE cohort study showed among 10.9% of 1087 patients at least one atherosclerotic vascular event either cardiac, cerebrovascular or peripheral vascular. The prevalence of coronary events was as follows: myocardial infarction – 2.2%, angina – 7.2% and sudden death – 0.3% (Urowitz et al., 2007). Comparable results provided large lupus cohorts studies in Pittsburgh and Baltimore showing the occurrence of clinical symptoms of coronary artery disease in 6.6% and 8.3% patients respectively (Manzi et al, 1997; Petri et al, 1992).

Study performed in 129 SLE patients at Department of Rheumatology and Internal Diseases Pomeranian Medical University, which focused on prevalence and selected risk factors of ischemic heart disease and myocardial infarction, demonstrated ischemic heart disease in 20 (15.5%) SLE patients and myocardial infarctions in 9 (6.97%). Ischemic heart disease and myocardial infarction were related to high activity of SLE, odds ratio (OR): 7.18; p = 0.012 and OR: 27.3; p = 0.006 respectively. Ischemic heart disease was significantly more common in older patients (52.8 years versus 42.2 years; p = 0.0008), in patients with hypertension (p < 0.05) and with impaired glucose tolerance (OR: 8.44; p = 0.03). Myocardial infarction was significantly associated with high uric acid level (OR: 5.01; p = 0.052) and impaired glucose tolerance (OR: 7.42; p = 0.047) (Ostanek et al., 2006a).

Our next study was aimed at the assessment of cardiovascular abnormalities in SLE patients in echocardiographic examination. The following pathologies were significantly more
frequent in SLE patients: pericardial involvement (58%), organic changes of the mitral valve cusps (54%), organic changes of the aortic valve cusps (36%), widening of the aortal lumen (35%), enlargement of the atrium (18%), hypokinosis of the left ventricle myocardial muscle (15%). Moreover, pericarditis was marker of high activity of the disease (OR: 3.89; 95% confidence interval (CI): 1.05-14.40; p = 0.042) and enlargement of the left atrium was significantly associated with the low level of HDL-cholesterol (OR: 6.94; 95%CI: 1.17-40.9; p = 0.033) (Ostanek et al., 2006b).

These data clearly show that cardiac involvement is a frequent and early systemic complication in the course of SLE. Cardiovascular disorders are often associated with high activity of the disease and classic risk factors are poorly related to these manifestations.

Additionally, many reports on subclinical atherosclerosis development in SLE patients have been published in recent years. Early diagnosis of subclinical changes can be established using noninvasive imaging techniques, which enable to assess atherosclerotic lesions on different stages of their development. The subclinical atherosclerosis was reported in 30% to 67% of SLE patients (Manzi et al., 1999; Fischer, 2008).

Endothelial dysfunction is a widespread phenomenon which represents an early stage of atherogenesis and it is established as a precursor and denominator of atherosclerotic events (Celermajer et al., 1992). Techniques designed to assess endothelial function are based on measurement of brachial artery reactivity in response to changes in blood-flow caused by passive congestion (flow-mediated vasodilatation, which is dependent on endothelial function) (Corretti et al., 2002). Studies performed in SLE patients documented an impaired endothelial function and this fact was attributed to reduced nitric oxide bioavailability resulting from increased oxidative stress in the course of SLE (El-Magadmi et al., 2004; Kiss et al., 2006; Wright et al., 2006). Furthermore, impairment of endothelial function remained significant even after adjustment for other classic atherosclerosis risk factors and the authors suggested that SLE is an independent risk factor for endothelial dysfunction (El-Magadmi et al., 2004). Interestingly, study completed in young females with SLE (mean age 29.4 years) disclosed vasomotor dysfunction of the coronary arteries, thus indicating the presence of subclinical coronary artery disease in these patients (Hirata et al., 2007).

Early stage of atherosclerosis can be also defined as a reduction of vascular elasticity. Measurement of pulse wave velocity is the most commonly used approach to assess stiffness of the large arteries (Tanaka et al., 1998). Evaluation of aortal wall elasticity in patients with SLE was the subject of numerous clinical studies. They all documented increased aorta stiffness in SLE patients and its relationship to a higher risk of cardiovascular events (Selzer et al., 2001; Bjarnegård et al., 2006) and its association with active inflammation in analyzed patient groups (Roman et al., 2005).

Ankle-brachial index measurement enables to identify atherosclerotic lesions in the arteries of the lower extremities. Because of its simplicity and low cost it is recommended for use in routine diagnostic evaluation especially to detect asymptomatic atherosclerotic lesions. Furthermore, this test is used in the stratification of overall cardiovascular risk (Graham et al., 2007). Clinical studies confirmed the usefulness of ankle-brachial index in detecting early atherosclerotic changes in SLE patients (Theodoridou et al., 2003).

Measurement of carotid intima-media thickness (CIMT) with B-mode ultrasound is a surrogate marker of atherosclerosis. The utility of CIMT in the evaluation of subclinical
Atherosclerosis in SLE patients has been well documented (Svenungsson et al., 2001; Doria et al., 2003; Fischer, 2008). This method is often used in epidemiological studies (Denarié et al., 2000; Sun et al., 2002) and also in assessing total cardiovascular risk (Ebrahim et al., 1999). Emphasis is put on a correlation between CIMT and the development of coronary artery disease (O’Leary et al., 1999; Takashi et al., 2002) and cerebrovascular manifestations (Chambless et al., 2000; Touboul et al., 2005). These findings were supported by our study, which also disclosed association between high cumulative dose of glucocorticosteroids and CIMT as well as carotid plaques development and confirmed less significance of classic risk factors for atherosclerosis in SLE patients (Fischer, 2008).

We also showed the clinical usefulness of vascular resistance assessment in SLE patients. Our study conducted in 92 patients was based on high resistance index measurement, which was calculated from Doppler spectrum of the popliteal arteries. Significantly lower values of high resistance index were observed in SLE patients, especially those with coexistence of APS, compared with the controls. This indicates that high resistance index measurement can be used to evaluate early, subclinical lesions in vessels in the course of SLE (Walecka et al., 2004).

The detailed analysis of noninvasive imaging techniques and their usefulness in early, subclinical atherosclerotic changes detection in SLE patients is reviewed elsewhere (Fischer & Brzosko, 2009). However, from this short description it can be concluded that lupus patients are at high risk of atherosclerosis as well as cardiovascular disorders development. Atherosclerotic lesions at an initial stage can be detected by means of increasingly sophisticated diagnostic tools, which allow evaluating systemic atherosclerosis, and they should represent an essential component of the diagnostic evaluation of SLE that is necessary to implement appropriate preventive and therapeutic procedures.

Furthermore, studies performed in children and adolescents with SLE strongly evidenced the premature atherosclerosis development in the course of the disease. On the other hand, they also suggest necessity of vascular testing with different imaging methods (Schanberg et al., 2009; Boros et al., 2011). Moreover, the authors emphasized a significant impact of applied treatment on atherosclerotic lesions development (Schanberg et al., 2009) and lipids’ metabolism (Boros et al., 2011) in pediatric SLE. Traditional risk factors predictive of increased atherosclerotic risk, similarly like in adult SLE patients, had limited clinical significance (Schanberg et al., 2009).

Understanding risk factors in the development of atherosclerosis in the course of SLE, especially those associated with the disease process, and early identification of patients at risk will enable to avoid irreversible cardiovascular damage, which represents the primary cause of morbidity and mortality in SLE patients.

### 3. Association between atherosclerosis and antiphospholipid antibodies in systemic lupus erythematosus – Related mechanisms

#### 3.1 Antiphospholipid antibodies and lupus-related atherosclerosis – Clinical studies

Accelerated atheromatosis is a well recognized clinical problem in SLE patients. Systemic lupus erythematosus has been considered an independent risk factor for endothelial dysfunction, an early stage in atherogenesis (El-Magadmi et al., 2004), and an increased CIMT (Colombo et al., 2007). Because the cardiovascular risk factors in SLE significantly
differ from those in the general population, many clinical as well as experimental studies investigated the role of SLE-related immune and inflammatory mechanisms of cardiovascular involvement.

The analysis of preclinical vascular disease in SLE and primary antiphospholipid syndrome (PAPS) patients showed higher prevalence of carotid plaque in SLE patients with coexistent APS than in patients with PAPS. However, the relationship with aPL (anticardiolipin antibodies – aCL and lupus anticoagulant – LA) was not found (Jiménez et al., 2005). On the other hand, the study performed in 200 SLE patients focused on evaluation of classic and lupus-related factors associated with CIMT and carotid plaque showed that aPL (aCL and/or LA) are independent risk factors for subclinical atherosclerosis (Ahmad et al., 2007). The multiethnic cohort study LUMINA which determined the baseline risk factors associated with the subsequent occurrence of vascular events (cardiovascular, cerebrovascular and peripheral vascular) confirmed aPL as independent predictors of these complications (OR = 4.7; 95%CI: 1.8-13.2) (Toloza et al., 2004). Similarly, study of longitudinal cohort of SLE patients also found aPL, and especially anti-beta2-glycoprotein I antibodies (aβ2-GPI) and aCL, baseline predictors of the first ever cardiovascular event (Gustafsson et al., 2009). Interestingly, an investigation performed in rheumatoid arthritis patients (premenopausal women, non-diabetic, non-hypertensive) disclosed advanced atherosclerosis in these patients shown as an increase of CIMT and plaque formation. Antiphospholipid antibodies (aCL and aβ2-GPI) were significantly more frequent in patients group supporting an idea that these antibodies represent an important risk factor for atherosclerosis in patients with rheumatoid arthritis (Pahor et al., 2006).

In accordance, our study on subclinical atherosclerosis in SLE patients which analyzed many serologic markers of the disease including aPL (aCL, LA, aβ2-GPI, anti-prothrombin antibodies (aPT) and aoxLDL) disclosed interesting association between CIMT and selected aPL. The presence of both isotypes of aCL IgG or IgM, LA and aPT IgA significantly increased the risk of thickening of intima-media and the relative risk was 4.4 (95%CI: 1.3-14.9), 4.0 (95%CI: 1.1-19.4) and 5.5 (95%CI: 1.1-30.2), respectively. We also confirmed the relationship between coexistence of APS and early atherosclerotic abnormalities in analyzed patients group. Additionally, the presence of aCL IgM significantly influenced carotid atherosclerotic plaque development (OR = 3.8; 95%CI: 1.1-13.1) (Fischer et al., 2007). Furthermore, our evaluation of risk factors for ischemic heart disease and myocardial infarction in SLE patients showed that these manifestations were more frequent in patients with coexistent APS (OR = 4.2 and 12.8, respectively). Ischemic heart disease was associated with aCL IgG (OR = 2.9) and myocardial infarction with aCL IgG and/or IgM (OR = 5.6) (Ostanek et al., 2006a). Furthermore, our next study on echocardiographic assessment of cardiovascular abnormalities documented a significant association between mitral valve involvement and aβ2-GPI IgA (OR = 13.63; 95%CI: 1.2-139.8) as well as aPT IgA (OR = 17.5; 95%CI: 1.3-231.0). Anticardiolipin antibodies IgG were significantly related to the increased amount of pericardial fluid (OR = 2.5; 95%CI: 1.1-6.1) (Ostanek et al., 2006b).

An investigation undertaken to examine the relationship of aPL with valvular, myocardial and arterial disease in SLE also documented significant correlation with mitral valve nodules and mitral regurgitation. Though, aPL were not related to myocardial hypertrophy,
systolic dysfunction, coronary or carotid atherosclerosis and other analyzed vascular abnormalities (Farzaneh-Far et al., 2006).

Current studies also did not prove any association between aPL and atherosclerosis in SLE patients. Results from the Hopkins’ Lupus Cohort regarding the relation of aPL (aCL, LA and aβ2-GPI) to thrombosis and non-thrombotic manifestations as well as atherosclerotic changes disclosed their significant relationship with venous and arterial thrombosis and selected cerebrovascular complications. Lupus anticoagulant was a sole antibody associated with myocardial infarction but there was no connection between aPL and CIMT, plaques and coronary calcification (Petri, 2010). In addition, the investigation focused on risk factors for coronary artery disease performed in SLE patients of the LASER study did not confirm any relation of aPL to cardiovascular risk (Haque et al., 2010).

3.2 Selected pathomechanisms in atherogenesis – The role of antiphospholipid antibodies

In regard to contrary reports from clinical studies there is large evidence that aPL may display proatherogenic effects which was disclosed by in vitro and in vivo studies.

Paraoxonase, an enzyme present in the arterial wall and in the HDL particle, inhibits LDL oxidation and is the major contributor to the antioxidant defense of plasma (Ames et al., 2009b). The paraoxonase gene is located at q21-q22 on the long arm of chromosome 7 (Durrington et al., 2001). It was shown in animal model that mice in which the paraoxonase gene was removed are devoid of protection against lipid peroxidation and HDL isolated from these mice were unable to prevent LDL oxidation in a co-cultured cell model of the artery wall (Jara et al., 2003). Furthermore, another experiment on non-lupus murine model investigated whether aCL could affect oxidant/antioxidant balance as an early biochemical step of APS. This study documented that aCL are associated with the decreased paraoxonase activity and reduced nitric oxide (sum of nitrite and nitrate) levels (Delgado Alves et al., 2005).

The study performed in SLE and PAPS patients paid attention to prevalence of anti-high-density lipoprotein antibodies (aHDL) and their relationship with aCL, aβ2-GPI and paraoxonase activity. Patients with SLE had decreased levels of HDL and its subfraction HDL₂ and HDL₃ and this lipoprotein or some of its components may represent target antigens for aHDL, which were significantly elevated in both analyzed patients groups. Moreover, there was strong inverse correlation between aHDL IgG and paraoxonase activity in SLE patients. In PAPS group, paraoxonase activity was inversely correlated with aCL IgG, aβ2-GPI IgG and IgM. However, on the basis on multiple regression model only aβ2-GPI IgG were found an independent predictor of decreased paraoxonase activity (r = -0.483, p = 0.003). The reported interactions may be relevant to the development of atherosclerosis in SLE and PAPS (Delgado Alves et al., 2002). Other observations also supported findings on the role of paraoxonase activity in SLE-related vascular abnormalities. The significantly decreased paraoxonase activity was found in SLE patients as compared to controls. Notably reduced paraoxonase activity was shown especially in lupus patients suffering from cardiovascular and cerebrovascular events (angina pectoris, myocardial infarction, transient ischemic attack, ischemic stroke) as compared to patients without such manifestations. Interestingly, also disturbed microcirculation was significantly associated with reduced
paraoxonase activity in patients with Raynaud’s phenomenon. These observations suggest that decreased paraoxonase activity in SLE patients may have pathogenic significance in accelerated atherosclerosis and its complications development (Kiss et al., 2007). More recent study evaluated vascular structure and function in women with aPL and assessed their relationship with paraoxonase activity. Patients with aPL in comparison with the controls had greater CIMT and arterial stiffness measured by pulse wave velocity, and lower flow-mediated dilatation pointing out an impaired endothelial function. Paraoxonase activity was lower in women with aPL than in controls and was inversely associated with CIMT and pulse wave velocity in these patients. Additionally, it was proved that HDL from women with aPL reduced nitric oxide bioavailability. That group was found to have an impaired anti-inflammatory and antioxidant properties (Charakida et al., 2009).

Some experimental studies clearly pointed out that aPL may enhance the development of atherosclerosis by oxidative modification of lipoproteins [LDL or Lp(a)] and by promoting the uptake of subendothelial lipoproteins by macrophage scavenger receptors causing an excessive intracellular accumulation of oxLDL and foam cell formation (Bassi et al., 2007). Oxidized LDL has chemotactic, proinflammatory and toxic properties, and promotes T-cell activation (Frostegård, 2005). The presence of oxLDL in atherosclerotic lesions in animal models and in humans has been shown (George et al., 2000). Enhanced oxidative stress and lipid peroxidation were also demonstrated in SLE patients (Frostegård, 2005).

A number of studies were addressing to the role of aoxLDL in atherosclerosis development in SLE patients. In our study we did not find any association between subclinical atherosclerotic lesions and these antibodies (Fischer et al., 2007). Other reports also provided discrepant results. The study of SLE patients in which aoxLDL and antibodies against oxidation epitopes in LDL were assessed showed aoxLDL more frequent in SLE patients with a history of cardiovascular disease in comparison to the controls (Svenungsson et al., 2001). It was also demonstrated that the titres of these IgG antibodies are high in SLE patients and that there is a good correlation between aoxLDL levels and the maximum intima-media thickness (Doria et al., 2003). High titres of aoxLDL IgG were also found in hypertensive SLE patients (Radulescu et al., 2004). On the other hand, the analysis of aoxLDL in SLE patients with and without APS, although, documented high frequency of aoxLDL in SLE patients with coexistent APS (not with PAPS) but did not find evidence suggesting that these antibodies may be associated with atherosclerosis. However, weak significant correlation between aoxLDL IgG and aCL IgG as well as aP2-GPI IgG and association with a history of venous thrombosis were confirmed (Hayem et al., 2001).

Noteworthy, a number of early studies performed in the general population showed that aoxLDL are associated with myocardial infarction (Erkkilä et al., 2000) and, moreover, the effect was independent of LDL-cholesterol levels (Puurunen et al., 1994). Similarly, in patients with early-onset peripheral vascular disease the titres of aoxLDL were increased. There was also an interesting tendency for higher antibody levels in patients with more extensive atherosclerotic lesions (Bergmark et al., 1995). On the contrary, there are even reports on an inverse correlation between aoxLDL titre and CIMT (Fukumoto et al., 2000). More detailed analysis indicated that in humans aoxLDL are low at an early stage of cardiovascular disease development in nonautoimmune disease and in healthy individuals but they are increased at later stages and in more advanced disease (Frostegård, 2005).
Furthermore, these antibodies are heterogeneous in immunoglobulin class and in their epitope specificity and affinity. Thus, present opinion indicates that IgG aoxLDL antibodies seem to be pathogenic for subclinical atherosclerosis development in SLE patient (Bassi et al., 2007). While, IgM aoxLDL are thought to provide protection against proinflammatory oxidized moieties, which was shown in animal models (Matsuura et al., 2006a).

Crossreactivity between selected aPL and aoxLDL is an additional issue. Cardiolipin was found a component of LDL and the crossreactivity of aCL and aoxLDL has been documented (McMahon & Hahn, 2007). In addition, in vitro macrophage uptake of oxLDL has been significantly enhanced in the presence of beta2-glycoprotein I (β2-GPI) and aβ2-GPI IgG (Hasunuma et al., 1997). The macrophage uptake of liposomes containing β2-GPI ligands also has been demonstrated indicating the possible proatherogenic role of aβ2-GPI IgG (Matsuura et al., 2005). The in vitro interaction between oxLDL and β2-GPI occurs quickly and evolve into stable covalent bonds making the complexes nondissociable. The similar mechanism has been postulated in vivo in the intima of arterial wall. Circulating oxLDL/β2-GPI complexes were demonstrated in SLE patients. In vitro investigations showed enhanced macrophage uptake of IgG immune complexes with oxLDL/β2-GPI. Measurement of oxLDL/β2-GPI complexes may represent a more physiological, clinically relevant, and accurate way of assessing oxidative stress and atherogenesis (Lopez et al., 2007).

The prolonged persistence of oxLDL/β2-GPI complexes can stimulate immune mechanisms and antibody production (aoxLDL/β2-GPI) that contribute to atherosclerosis (Lopez et al., 2007). The study performed in patients with selected systemic connective tissue diseases including SLE and APS showed aoxLDL/β2-GPI IgG significantly increased in SLE patients. Significantly higher levels of these antibodies were also confirmed in SLE patients with coexistence of APS with a positive predictive value for APS of 90%. Moreover, the predictive value for arterial thrombosis was 94%. It was considered that the presence of circulating oxLDL/β2-GPI complexes and IgG antibodies to these complexes indicates significant vascular injury and oxidative stress and proved an active role of autoimmune-mediated atherothrombosis (Matsuura et al., 2006b). Further studies disclosed contribution of these complexes and related antibodies to organ damage (especially renal involvement) and confirmed their association with thrombotic events in SLE patients (Bassi et al., 2009). Their relationship with both CIMT and reduced paraoxonase activity in PAPS patients has been also demonstrated (Ames et al., 2006).

Antiphospholipid antibodies may also have a direct effect on endothelium. Early in vitro studies documented that IgG from patients with high titre of aCL enhanced monocyte adhesion to human umbilical vein endothelial cells via mechanism dependent on β2-GPI (Simantov et al., 1995). Additionally, aβ2-GPI mediates binding of aCL to endothelial cells leading to their activation, and contributing to thrombosis and thrombocytopenia in patients in whom aCL were present (Le Tonquéze et al., 1995).

The other atherothrombotic mechanism has been also postulated based on decreased binding of annexin V to endothelial cells in the course of SLE. Among analyzed antibodies aCL IgG significantly influenced this decreased binding. Moreover, there was a positive association between annexin V binding and CIMT (r = 0.73, p < 0.001). Interestingly, immunochistochemical analysis revealed presence of annexin V in all human atherosclerotic plaques tested, especially at sites prone to rupture (Cederholm et al., 2005). The novel in
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Vitro findings confirmed these observations showing reduced annexin A5 binding to endothelium by monoclonal aCL IgG via dose-dependent mechanism. Of note, preincubation of intravenous (IV) immunoglobulins at therapeutically relevant doses with aPL and monoclonal aCL restored annexin A5 binding to comparable levels when normal healthy serum was used. On the contrary, IV immunoglobulins per se reduced annexin A5 binding to endothelial cells when added to normal healthy serum suggesting that some antibodies in IV immunoglobulins may be involved in atherothrombosis and cardiovascular disease development during IV immunoglobulins treatment (Frostegård et al., 2010). The study conducted to investigate the association of plasma annexin V, anti-annexin V antibodies and aCL with acute myocardial infarction showed that patients suffering from acute myocardial infarction had significant low levels of annexin V and high levels of antibodies to this protein (p = 0.002 and p = 0.004, respectively). This combination indicated a hypercoagulable state in patients with acute myocardial infarction which was not related to traditional cardiovascular risk factors because plasma antibodies and annexin V levels were not correlated with hypertension, diabetes mellitus, hyperlipidemia, gender, age and smoking habits (Shojaie et al., 2009).

Antiphospholipid antibodies may act at various stages of atherogenesis process: activating endothelium, mediate adhesion of leukocytes and potentiating the uptake of oxLDL by scavenger receptor to generate foam cells. Crossreactivity of aPL to lipoprotein antigens may further facilitate atherogenesis (Narshi et al., 2011). However, SLE characteristics can mask the pathogenic role of some of autoantibodies in the development of atherosclerosis (Bassi et al., 2007). Therefore, the utility of aPL in related to SLE cardiovascular risk estimation in clinical practice remains controversial.

4. Atherosclerosis in primary antiphospholipid syndrome

Primary antiphospholipid syndrome is a systemic autoimmune disease characterized by the occurrence of arterial or venous thrombosis or pregnancy complications together with the persistence of aPL in the absence of other known autoimmune conditions (Miyakis et al., 2006).

Although, an accelerated atherosclerosis in APS coexistent with SLE is a well known clinical problem (Fischer, 2008; Belizna et al.; 2007; Roman et al., 2001). In patients with PAPS arterial ischemic events may occur even in the absence of evident atherosclerosis. Therefore, there is the risk of misdiagnosing young patients with potentially life-threatening symptoms including myocardial infarction (Gualtierotti et al., 2011). Furthermore, recent reports showed that a number of PAPS patients can develop Syndrome X defined as a condition with the presence of angina-like chest pain, positive response to stress testing and normal coronary angiograms often existing in the absence of traditional cardiovascular risk factors. It is suggested that microvascular abnormalities secondary to endothelial dysfunction may cause this complication development (Sangle et al., 2008).

Accordingly, there is accumulating evidence to confirm an impaired endothelial function in the course of PAPS. The study performed in 31 young patients with PAPS (mean age 35 years) documented a significant endothelial dysfunction in comparison with the controls. Moreover, patients with arterial involvement had importantly more prominent decrease of flow-mediated dilatation in comparison with patients with venous involvement. The
presence of classic atherosclerotic risk factors did not differ between patients and the control group. Additionally, association between aCL IgG/IgM as well as variety of therapy and impaired endothelial function was not confirmed (Mercanoglu et al., 2004). Similarly, another study in which parameters of endothelial dysfunction were analyzed also proved endothelial dysfunction in 25 PAPS patients and, in addition, showed significant inverse correlation between endothelial dysfunction and selected markers of endothelial activation/damage (Štalc et al., 2006). In contrast, another group did not show in 20 PAPS patients neither impaired endothelial function, pathological values of plasma markers of endothelial or platelet activation nor progenitor and mature endothelial cells, suggesting that the alteration leading to thrombosis in PAPS concerns primarily the clotting system (Gresele et al., 2009). On the other hand, results showed in 44 PAPS patients in whom subclinical atherosclerosis was evaluated by endothelial function assessment and CIMT measurement clearly documented both abnormal values of CIMT and parameters of endothelial function. Moreover, there was negative linear correlation between flow-mediated vasodilation and CIMT. The von Willebrand factor level was also significantly higher in PAPS patients than in the control group, reflecting an endothelial injury. Similarly to other reports, significant difference regarding traditional cardiovascular risk factors between PAPS patients and the controls was not shown. Moreover, there was no correlation between impaired endothelial function and aPL serum levels. The authors pointed out that a relationship exists between the presence rather than the amount of aPL and subclinical atherosclerosis (Der et al., 2007). However, study performed in subjects with idiopathic aPL showed association between aCL IgG titre and CIMT. In addition, it confirmed aCL IgG as well as homocysteine and fibrinogen as independent predictors of CIMT indicating that measurement of homocysteine and fibrinogen may help to identify aPL patients who are more likely to develop atherosclerosis (Ames et al., 2002). More recent studies also confirmed a usefulness of CIMT measurement in a detection of early atherosclerotic changes and showed an association between CIMT and aPL in thrombotic PAPS patients (Ames et al., 2009a) as well as in patients with APS secondary to SLE (Belizna et al., 2008). Furthermore, a relationship between increased CIMT and stroke in the course of PAPS was reported (Medina et al., 2003).

A number of studies confirmed a clinical utility of other noninvasive imaging methods in atherosclerosis diagnosis in PAPS patients showing increased arterial stiffness (Belizna et al., 2008; Charakida et al., 2009) or abnormal ankle-brachial index (Barón et al., 2005).

Epidemiological data from a multicenter, consecutive, prospective study on 1,000 APS patients disclosed at disease onset that some of the most common manifestations were cerebrovascular disorders (stroke – 13.1% and transient ischemic attack – 7.0%). Myocardial infarction was present in 2.8% of patients. Though, cumulative clinical features during the evolution of disease showed a higher prevalence of both neurologic manifestations (including stroke – 19.8% and transient ischemic attack – 11.1%) as well as selected cardiac complications – myocardial infarction (5.5%), angina (2.7%) and coronary bypass rethrombosis (1.1%) (Cervera et al., 2002). Myocardial infarction and stroke were also the most common causes of death in this cohort (18.9% and 13.2% respectively) (Cervera et al., 2009). Accelerated atherosclerosis in the course of PAPS should be considered an example of atherothrombotic event caused by aPL playing both proatherogenic and prothrombotic role.
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Selected cardiovascular complications can exist without overt atherosclerosis (Gualtierotti et al., 2011). Therefore, early diagnosis of subclinical atherosclerotic changes with different imaging methods is extremely important.

5. Relationship between antiphospholipid antibodies and atherosclerosis in the general population

The new theories developed in the last century enabled the better understanding of atherosclerosis pathogenesis. The “response-to-injury” theory formulated by Ross and Glomset in 1973 showed endothelial damage to be a key initiator of atherosclerotic lesions. Further investigations disclosed that endothelial cells have the potential to play an active role both in the formation of lipid-laden foam cells and in the accumulation of necrotic tissue which are hallmarks of the atherosclerotic lesion (DiCorleto & Chisolm, 1986). The role of immunological and inflammatory factors in the pathogenesis of atherosclerotic lesions was confirmed in the 1990s (Ross, 1993). The interplay of inflammatory and immunological mediators including cytokines, chemokines, adhesion molecules, leukocytes, complement as well as antibodies, promotes damage of endothelium and progressive atherosclerotic plaque development (Hansson, 2001).

The potential role of aPL in atherosclerosis and atherosclerotic vascular events development in the general population has been extensively studied over the last few decades.

A case-control study, which included patients operated on for atherosclerotic peripheral vascular disease before 50 years of age, tested the hypothesis whether antibodies associated with an immune/inflammatory damage to the vascular wall were associated also with early atherosclerosis. Subjects were compared for the prevalence of aCL and anti-endothelial cell antibodies (AECA), classic risk actors for atherosclerosis and signs of inflammation. The presence of analyzed antibodies significantly differed between patients and controls (p < 0.05). The presence of aCL and AECA was confirmed in 14.5% and 12.9% patients, respectively. None of the patients with antibodies had clinical or laboratory features of systemic connective tissue disease. The patients had higher values of laboratory parameters suggesting inflammation. However, there was no correlation between the presence of antibodies and laboratory signs of inflammation. Interestingly, the occurrence of hyperlipidemia/dyslipidemia was lower in patients with aCL and/or AECA, as compared to patients without these antibodies suggesting that these antibodies have a role in vascular damage (Nityanand et al., 1995). These observations were confirmed by other investigators. The next study analyzed patients who had undergone elective suprainguinal (aortofemoral, femoral-femoral, iliac endarterectomy, or axillofemoral bypass grafting) or infrainguinal procedures for atherosclerotic occlusive disease. Patients were assessed for the presence of aPL- aCL IgG, IgM, IgA and LA and their association with the progression of the disease. There was statistically significant difference between aPL positive and negative patients in the progression of arterial occlusive disease in at least one artery during the 9 years follow-up (73% versus 37%, p < 0.0001). Furthermore, multivariate logistic regression analysis was used to test the effect of atherosclerotic risk factors on disease progression. Antiphospholipid antibodies status and traditional atherosclerotic risk factors, heart disease, chronic renal insufficiency, warfarin therapy and type of procedure were examined. Of note, only the presence or
absence of aPL significantly contributed to progression in those patients who had undergone elective lower extremity revascularization for chronic ischemia (Lam et al., 2001). Interesting study was performed in 411 patients with atherosclerotic vascular disease who underwent at least one of the following events: unstable angina, myocardial infarction, angioplasty, coronary artery bypass surgery, claudication, transient ischemic attack and ischemic stroke. All subjects were tested for the presence of aCL IgG and IgM. It was shown on the basis of stepwise logistic regression analysis that for any atherosclerotic vascular disease event, significant independent, positive correlates included selected classic atherosclerotic factors (age, diabetes, male gender, hypertension and the family history of vascular atherosclerotic disease) and aCL IgM. Moreover, for those patients having a myocardial infarction, coronary bypass surgery and/or angioplasty, aCL IgM was a significant independent positive predictor of cardiovascular events. Additionally, aCL IgM was a positive significant independent risk factor for vascular events, including myocardial infarction, at ≤ 55 years of age. Levels of aCL IgG were positively associated with aCL IgM. The authors suggested that aCL IgG and IgM should be routinely measured as ancillary atherothrombotic risk factors in all patients with atherosclerotic vascular disease events, in patients at high risk of atherosclerotic vascular disease, and in patients where thrombosis is a major pathoetiolo(273x278)gy (Glueck et al., 1999). These results are consistent with the data from a prospective cohort study of the relation of aCL and risk of myocardial infarction and cardiac death performed in middle-aged men of Helsinki Heart Study. The levels of aCL IgG were significantly higher in subjects than controls (p < 0.005). Persons with the highest levels of aCL IgG were at 2-fold higher risk of myocardial infarction and the risk was independent of traditional risk factors for atherosclerosis (Vaarala et al., 1995). The clinical importance of high levels of aCL also documented study of patients with focal cerebral ischemia harboring aCL of at least 10 GPL units at the time of their index event. Patients were prospectively followed to estimate the effect of aCL titer on time to and risk of subsequent thrombo-occlusive events (stroke, transient ischemic attack, deep venous thrombosis, pulmonary embolism, myocardial infarction) and death. Patients with aCL titers > 40 GPL were younger, had more prior strokes, more frequent subsequent thrombo-occlusive events and death, and a shorter median time to event (Levine et al., 1997). The more recent study performed in 432 Taiwanese adults with cerebral ischemia disclosed an interesting impact of aCL IgG. Patients were classified into five subtypes according to the cause of cerebrovascular event: large-artery atherosclerotic disease, stroke of unknown etiology, small-artery occlusive disease, cardioembolism, and stroke of other known etiology. It was shown that aCL IgG selectively increases in patients with large-artery atherosclerosis and stroke of unknown etiology, reflecting selective activation of humoral immunity for aCL in the pathogenesis of cerebral ischemia (Chen et al., 2006). On the other hand, a multicenter cohort study performed in premenopausal women with a first myocardial infarction or ischemic stroke showed a significant relationship of LA to myocardial infarction (OR = 5.3) and ischemic stroke (OR = 43.1). Anti-beta2-glycoprotein I antibodies also were associated with an increased risk of ischemic stroke (OR = 2.3). However, neither aCL nor aPT affected the risk of those manifestations (Urbanus et al., 2009).

Finally, an inclusion of aPL to the estimation of risk of atherothrombotic vascular events development in the general population seems to be justified, especially in young patients without coexistent classic cardiovascular risk factors.
6. Selected non-criteria antiphospholipid antibodies and their relationship to atherosclerosis

Early studies performed in 1990s have already put attention to aPL directed against non-cardiolipin antigens in SLE. They documented significantly increased levels of selected aPL in lupus patients and described wide profile of potential antigens (Maneta-Peyret et al., 1991; Toschi et al. 1993).

Many studies on the clinical significance of aPT have been reported in APS patients (Galli & Barbui, 1999) and several pathogenic mechanisms providing to hypercoagulable state of APS via aPT were suggested (Atsumi & Koike, 2002). Interesting study performed in animal model provided the first direct evidence for thrombus induction by aPT. Mice were immunized with prothrombin, β2-GPI or β2-GPI followed by prothrombin. The presence of clinical manifestations of APS was analyzed. Thrombosis was studied in an ex-vivo model in which aorta was sutured for 1 minute and the presence or absence of visible thrombus was qualitatively evaluated. All prothrombin-immunized mice developed thrombus within the aorta confirming prothrombotic properties of aPT (Haj-Yahja et al., 2003). Moreover, the study performed in middle-aged men with dyslipidemia showed higher levels of aPT in patients who developed myocardial infarction or cardiac death than in controls. The relative risk of these complications was 2.5-fold higher (95% CI: 1.2-5.3) in patients with aPT (Vaarala et al., 1996). These data were supported by the investigation performed in young women with acute ischemic stroke. Anti-prothrombin antibodies were more frequent in patients with cerebrovascular manifestations in comparison with the healthy controls (OR = 182.0; 95% CI: 23.4-1416.6) and nonischemic neurological disorders patients (OR = 26.7; 95% CI: 5.7-123.7). In 43% of stroke patients aPT were the only antibodies detected (Cojocaru et al., 2008).

The clinical significance of these aPL was also intensively investigated in our studies. Our earlier reports demonstrated the usefulness of aPT in diagnosis of APS in SLE patients and the highest specificity showed aPT IgG (95.12%). Additionally, aPT IgG were significantly associated with selected central nervous system manifestations, and aPT IgM importantly influenced risk of development of cardiac complications and mononeuropathy. Interestingly, aPT IgA were significantly related to pleurisy and leucopenia, but they did not associate with the coexistence of APS (Ostanek et al., 2005). While, our study focused on atherosclerotic changes development in SLE patients disclosed a significant influence of aPT IgA and AECA on increase of CIMT (Fischer et al., 2007; Fischer et al., 2006). Moreover, this finding for aPT IgA was also confirmed by multivariate backward stepwise analysis (Fischer et al., 2007).

The analysis of other aPL in diagnosing APS and their role in main clinical complications related to APS showed that anti-phosphatidylserine antibodies (aPS) IgG and IgM are valuable diagnostic tool with a high significant predictive value for thrombotic events – arterial as well as venous (Lopez et al., 2004; Bertolaccini & Hughes, 2006; Szodoray et al, 2009). However, the case report of SLE patient with myocardial infarction and without associated traditional cardiovascular risk factors and classic aPL disclosed interesting relation to aPS IgA suggesting that complete evaluation for aPL should include testing for all three isotypes (Jansen et al., 1996). The data on an association between aPS and cerebrovascular disorders have been also frequently reported. The study which evaluated the relevance of different aPL in patients with cryptogenic stroke and with determined
causes of stroke displayed a significant role of aPS IgG and, interestingly, αβ2-GPI IgA in stroke etiology (Kahles et al., 2005). Similarly, it was shown in 203 patients suffering from ischemic stroke that, in addition to classic aPL, also aPS IgG may be considered risk factors for stroke (Saidi et al., 2009). The analysis of 250 persons with cerebral infarction (lacunar, atherothrombotic and cardiogenic cerebral embolism) including SLE patients disclosed, moreover, that in aPS or anti-phosphatidylinosit (api) positive patients an increase of CIMT as well as presence of carotid plaques and carotid stenosis ≥ 50% were more frequent. Among 250 patients, 13.6% were positive either αPS or αPI and 6.8% were positive for both. The majority of patients with αPS and/or αPI were negative for classical αPL (αCL, αβ2-GPI, LA). On the other hand, 70.6% of these patients were positive for antinuclear antibodies. The authors pointed out that aPL are a risk factor for cerebral infarction especially in SLE patients and in younger population (Okuma et al., 2010). Moreover, a significant association between CIMT and the risk of ischemic stroke has been well documented (Chambless et al., 2000; Touboul et al., 2005).

There is also an increasing evidence of a relationship between the clinical manifestations of APS and antibodies directed against phosphatidylethanolamine (aPE) (Mcintyre & Wagenknecht, 2000). These antibodies were also often reported as the only aPL particularly in patients suffering from thrombotic disease (Bérard et al., 1996; Sanmarco et al., 2001). Furthermore, these antibodies, especially IgG isotype, may contribute to detect more patients with aPL-related clinical manifestations in SLE patients and their significant correlation with valvulopathies and livedo reticularis in patients with SLE was reported (Balada et al., 2001).

The study performed in 185 patients, including SLE patients, suffering from stroke showed aPE in 35% of patients. Furthermore, the presence of aPE was the most frequent finding in patients who were suspected to have an associated APS (Gonzales-Portillo et al., 2001). The next study on young non-SLE patients without obvious causes of arterial thromboembolism who underwent ischemic cerebrovascular incidences also demonstrated the presence of wide profile of non-cardiolipin aPL, including aPE. However, the frequency of aPE was lower – 10.4% (Toschi et al., 1998). In addition, the finding of aPE in the cerebral spinal fluid of patient with a documented ischemic stroke may suggest a possibility of an intrathecal production of aPL in the course of central nervous system disorders. However, this observation needs to be confirmed by further investigations (Sokol et al., 2000). A number of reports confirmed also an association between aPE and atherosclerosis. The analysis of the clinical features of 20 patients with aPE only, among whom 17 had symptoms potentially related to APS, showed significant relationship between aPE and arteriosclerosis with peripheral arteriopathy (Desauw et al., 2002).

Finally, the association between wide profile of aPL including aPS, αPI as well as anti-phosphatidic acid antibodies and cardiac impairment in lupus patients was reported indicating an adjunctive pathogenic role of aPL in these complications (Amoroso et al., 2006).

This short description emphasizes that rare non-criteria aPL are associated with selected vascular disorders in the course of SLE. The determination of these antibodies may provide an additional tool for APS diagnosis and appears to be of interest in patients negative for the serologic markers of APS but presenting a clinical picture highly suggestive of this syndrome.
7. Management and monitoring of atherosclerosis and cardiovascular risk factors in systemic lupus erythematosus patients

European League Against Rheumatism published in 2010 recommendations for monitoring SLE patients in clinical practice and in observational studies. It is proposed to assess cardiovascular risk factors at baseline and during follow-up at least once a year. Although data from the literature have clearly shown that traditional cardiovascular risk factors cannot fully explain the increased incidence of atherosclerosis and its complications in this patients population, an agreement exists on the need for monitoring conventional risk factors and treating modifiable risk factors. The evaluation of cardiovascular risk includes: assessment of smoking, vascular events (cerebral/cardiovascular), physical activity, oral contraceptive, hormonal therapies and family history of cardiovascular disease, blood cholesterol, glucose, blood pressure and body mass index (and/or waist circumference). More frequent assessment may be required in certain situations, for instance, in patients on glucocorticosteroids therapy (Mosca et al., 2010).

The guidelines for risk factors management developed to prevent cardiovascular disease in SLE patients contain indications regarding ideal targets values for risk factors and recommended therapy (Table 1.) (Wajed et al., 2004).

| Risk factor       | Ideal target values                                      |
|-------------------|----------------------------------------------------------|
| Blood pressure    | < 130 mmHg systolic and diastolic < 80 mmHg              |
| LDL cholesterol   | < 2.6 mmol/l                                              |
| Diabetes mellitus | Fasting blood glucose < 7.0 mmol/l                       |
|                   | Random blood glucose < 11.0 mmol/l                       |
| Smoking           | Stop smoking                                             |
| Obesity           | Body mass index < 25 kg/m²                                |

Table 1. Summary of ideal targets for risk factors in patients with systemic lupus erythematosus (Wajed et al., 2004)

Subjects with SLE tend to develop hypertension more often than general population. The drugs indicated as a first line treatment of hypertension in SLE patients are diuretics and ACE agents. Treatment with ACE is also recommended for heart failure, coronary heart disease, ventricular hypertrophy or renal failure. These agents are protective of brain stroke or microvascular injury in the course of diabetes mellitus (Table 2). Aspirin is an agent of proven value in primary and secondary coronary heart disease. It seems to be beneficial in terms of survival for SLE patients. However, its universal role for SLE treatment is not proven yet, its use is indicated in specific situations like in subjects with previous cardiovascular events, smokers, subjects positive for aPL (Table 2) (Wajed et al., 2004).

Glucocorticosteroids are commonly used in SLE patients and their relation to the risk of developing atherosclerotic lesions is now well established (Manzi et al., 1999; McDonald et al., 1992). On the other hand, antimalarial drugs have been shown to have a beneficial effect in SLE (Rahman et al., 1999; Molad et al., 2002). Additionally, in patients with APS anticoagulation therapy is used. The long-therm antithrombotic therapy provides protection against thrombotic events, but it does not have an antiatherogenic potential (Der et al., 2007).
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Table 2. Specific recommendation for aspirin and ACE inhibitors in patients with systemic lupus erythematosus (Wajed et al., 2004)

Moreover, the addition of aspirin also has no significant benefit, so aspirin therapy may not be necessary in this group (Wajed et al., 2004).

Keypoints of APS diagnosis and treatment in patients with acute coronary syndrome are summarized in table 3 (Gualtierotti et al., 2011).

| Situations when the diagnosis of antiphospholipid syndrome should be taken into account in patients with acute coronary syndrome: | |
| --- | --- |
| - in young patients (< 55 years in men and < 65 years in women) | |
| - coronary arteries display normal angiography | |
| - there are no other traditional cardiovascular risk factors | |
| - there is no history of drug abuse | |
| - there are no other causes of heart diseases (congenital abnormalities, etc.) | |

Treatment of acute coronary thrombosis is not different in aPL-positive and aPL-negative patients

Anticoagulation with a target INR > 3.0 has been suggested in APS patients with arterial thrombosis

The persistent medium-high aPL is a risk for arterial recurrences and anticoagulation should be continued

The elimination or reduction of other cardiovascular risk is mandatory

There are no data to recommend additional treatments (aspirin, hydroxychloroquine, or statins, etc.)

Table 3. Antiphospholipid syndrome diagnosis and therapy in patients with acute coronary syndrome (Gualtierotti et al., 2011)

In aPL related atherosclerosis treatment may be directed at managing the effects of aPL or at decreasing their titer. In this regard, statins may be potent drugs with positive effect on the immune system, vascular endothelium, paraoxonase activity and reduction of inflammation (Ames et al., 2009b). Furthermore, biological therapies may be helpful to prevent atherothrombotic events in APS/SLE patients (Der et al., 2004). However, anti-CD20
accomplished so far lowering of aPL titers in some PAPS patients but not others (Ames et al., 2009b).

8. Conclusions

Patients with SLE are at risk of accelerated and premature atherosclerosis and cardiac complications development. Sensitive noninvasive imaging techniques enable to evaluate atherosclerotic changes at every stage of their development and should be commonly used for diagnosis and progression monitoring. Traditional risk factors fail to fully account for cardiovascular risk in SLE patients. Therefore much attention has been put to investigate the role of selected immune mechanisms involved in atherosclerotic lesions pathogenesis. A heterogeneous group of antibodies in SLE may accelerate the inflammatory process of atherosclerosis. There is a growing body of evidence that aPL may display proatherogenic effect in several in vitro and in vivo studies. However, clinical studies provided discrepant reports on association between aPL and subclinical atherosclerosis as well as cardiovascular manifestations in patients with SLE and large prospective studies are needed to establish the role of these autoantibodies in identifying patients at risk. Furthermore, management of SLE-related atherosclerosis still remains an unsolved issue. The official recommendations and guidelines are focused on traditional modifiable risk factors and conventional anticoagulation therapy. The identification of autoantibody biomarkers may provide a useful tool to recognize patients with subclinical changes and avoid an irreversible cardiovascular damage and, on the other hand, may help to identify new therapeutic goals.

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The antiphospholipid syndrome has been described for the first time by Graham Hughes in 1983 as a condition connected with thromboses or foetal losses and antiphospholipid antibodies presence. Form that time there has been a great progress in knowledge, including antiphospholipid antibodies characterisation, their probable and also possible action, clinical manifestations, laboratory detection and treatment possibilities. This book provides a wide spectrum of clinical manifestations through Chapters written by well known researchers and clinicians with a great practical experience in management of diagnostics or treatment of antiphospholipid antibodies' presence.

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