

Vasculopathy and vasculitis in systemic lupus erythematosus

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Abstract: Systemic lupus erythematosus (SLE) is an autoimmune connective tissue disease, where vascular lesions are one of the typical symptoms. The pathological process often involves skin vessels, renal glomeruli, the cardiovascular system, brain, lung alveoli, and gastrointestinal tract vessels. This review presents possible adverse mechanisms underlying the cause and effect relationship of various factors causing vascular lesions in SLE patients. The generally accepted hypothesis links vascular damage in SLE with the deposition of immune complexes in the vascular endothelium. The anti-endothelial cell antibodies (AECA), antiphospholipid antibodies and anti-double stranded DNA antibodies present in SLE, that directly or indirectly affect endothelial cells, causing inflammatory damage to the vessel wall, and their role, have been discussed. It has been stressed that although the suggested role of AECA in vasculitis pathogenesis has not been fully established, evidence, however, has demonstrated that AECA is a factor causing endothelial damage in SLE patients. On the other hand, issues concerning cellular adhesion molecules which enable leukocyte adhesion and rolling along the endothelial cell surface, and their extravascular migration, focus on the role they may be playing in SLE patients with vasculitis. A potential role of soluble forms of adhesion molecules, pentraxin 3, medications, infections in the pathogenesis of this disease has also been shown. Special attention has been given to the role of type 3 hepatitis virus in vascular damage in SLE.

Key words: antibodies adhesion molecules, drugs, systemic lupus erythematosus, vascular lesions

Vascular damage in humans develops on various grounds. It may be inflammatory or noninflammatory. The damages may be induced by environmental factors (toxic agents, medications, microorganisms), through cancer as a paraneoplastic syndrome, or may be directly associated with an active immune process. Systemic lupus erythematosus (SLE) is a connective tissue autoimmune disease, where vasculopathy is one of the typical symptoms [1]. It is reported in 10–40% of patients. It occurs more often in women (80%) than in men and may precede the development of a full-blown SLE [2,3].

The differentiation of the type of vascular complications is very difficult, sometimes impossible, and requires an in-depth immune, histopathologic and imaging diagnostic approaches, and extensive clinical experience. It may play a key role in the choice of treatment strategy and prediction of the patient prognosis. Therefore, the awareness of the etiology, pathophys-

iology, the clinical and histopathological setting, and SLE associated vascular complications is of great clinical significance.

Vascular lesions in SLE are commonly known as the lupus vasculopathy; a typical lupus vasculitis with inflammatory and vascular wall necrosis and a thrombus in the lumen of affected artery occurs less often [4–6]. Appel et al. [4,5] provided an SLE vasculopathy classification including: non complicated vascular deposits of immune complexes, noninflammatory necrotic vasculopathy, thrombotic microangiopathy and true lupus vasculitis. Of all lupus vasculitis, cases more than 60% is leucocytoclastic inflammation, 30% is vasculitis with cryoglobulinemia, and systemic vasculitis resembling polyarteritis nodosa constitutes about 6% of SLE vasculitides patients [3,5,7–9]. Other clinical syndromes of vasculopathy in patients from the discussed group include thrombocytopenia with thrombotic purpura, venous thrombosis, antiphospholipid syndrome and urticaria vasculitis, reported in 5% of SLE patients [3,5].

The systemic lupus erythematosus associated vasculitis may present different clinical courses. The broad spectrum of symptoms includes mild forms affecting only cutaneous vessels, and also severe, catastrophic forms, with organ complications development, and vasculitis within the internal organs [1,10,11]. Lupus vasculopathy is usually seen in cutaneous

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vessels, in renal glomeruli, coronary and brain vessels, the brain, lung alveoli and less often in the gastrointestinal tract [1]. It has to be stressed that cutaneous lupus vasculopathy in SLE occurs most often, and is reported in 94% of patients with lupus vasculitis [3,12,13]. Mild forms are characterized by purpura, urticaria lesions or bullous lesions of extremities, and livedo reticularis on the trunk [3]. With a more severe course, digit ulcerations and necrosis of the nail bed occur, and cryoglobulinemic vasculitis coexists with cutaneous lesions [1,3,14]. Clinically, 40% of cutaneous lesions have the form of discoid erythematosus lesions usually located on fingertips, 30% have the form of the erythema of the hand dorsum, and 20% of them are nodular lesions [3]. Five percent of patients experience subcutaneous vasculitis [3,5].

It has been demonstrated that internal organ vessels are affected in 18% of SLE vasculitis patients [3]. Renal vasculitis takes the shape of focal segmental glomerulitis with development of fibrinoid necrosis [1]. Lung vasculitis takes the form of necrotic alveolar capillaritis predisposing to pulmonary hemorrhage [1]. Brain vasculitis occurs only in about 10% of SLE patients, and associated clinical symptoms are very variable; from a mild cognitive dysfunction to severe psychosis and convulsions, local ischemia and strokes [1,15]. The peripheral nervous system may also be affected by lupus vasculopathy leading to multifocal inflammatory mononeuropathies [1]. Mesothelium vasculitis may also occur and lead to gastrointestinal hemorrhage or perforation [1].

Pathophysiology of vasculopathy and vasculitis in SLE

Vasculopathy in SLE and in other autoimmune systemic diseases and infections is secondary vasculitis [11], however the pathogenesis of these diseases has not been fully elucidated [12].

As mentioned above, SLE vasculopathy may be of inflammatory or thrombotic origin [1]. Both mechanisms involve the immune system, and the activation and consequent endothelial lesions play a very important role in the disease pathogenesis [1,16]. It seems that endothelial cells activation with pronounced expression and activation of adhesive molecules are the key factors in the pathogenesis of this disease [12,16]. Activated endothelial cells are able to bind various proteins and cells to the vessel wall [12]. This process is at first limited only to postcapillary venules, which are often affected in the small vessel disease [12]. However, vasculitis localization in arterial branching is most probably the result of compression forces [12]. The damage localization may also depend upon the hydrostatic pressure values and local blood circulation disorders [12].

The common hypothesis for SLE vasculopathy concerns the endothelial deposition of circulating immune complexes [11]. The consequent, secondary inflammatory response activates the complement cascade, most probably with C5b-9 complex formation, destroying vascular basal membranes [1]. How-

ever, there are also other mechanisms causing the immune response antigen to be primarily located in the vessel wall [11]. For example, the nucleo-histone adhesion to the vessel basement membrane in lupus nephritis results in secondary antibody binding, and the locally formed complex may be the cause of immune vasculitis [11]. Moreover, the immune complexes clearance decreases, and the tissue factor expression is upregulated which also may contribute to lupus SLE vasculopathy [17]. Most probably, also the C1q complement component and its receptor in the endothelial cellular membrane may take part in endothelial activation/damage [15,16]. Another complement system component, C5a, may induce endothelial release of heparan sulfate acid, that produces a prothrombotic effect in lupus vasculitis [15].

There are many various autoantibodies in SLE as circulating immune complexes, which directly or indirectly affect endothelial cells, causing chronic vessel wall damage [16,17]. The activation and damage of endothelial cells and the associated monocyte adhesion is caused particularly by antibodies directed against endothelial cells and cell membrane phospholipids [18].

Systemic vasculitis in SLE is proatherogenic condition and is characterized by leukocytes activation, and production of cytokine and other inflammatory mediators [16,17,19].

Anti-endothelial cell antibodies

Anti-endothelial cell antibodies (AECA) occur in over 80% of SLE patients [20,21]. It seems that their presence is typical of vasculitis and vascular thrombosis and lupus nephritis. These antibodies rarely cause a simple cytotoxic effect; they have a complex, immune process dependent effect [22].

It has been reported that AECA belong to the G, M and A immunoglobulin classes [20] and bind to antigens through the F(ab)₂ region [1]. The structure of these antigens has not been, however, fully determined [1,22,23]. It has been demonstrated that they are constitutive surface proteins of 25 to 200 kDa molecular mass [22], different from class II human leukocyte antigen (HLA) or blood group antigens [1]. The following endothelial cell antigens that react with AECA, are: heparin-like compounds, DNA and DNA-histon complexes, PO and L6 ribosome protein, elongation factor 1 α , adenyl cyclase associated protein, profilin II, plasminogen activator inhibitor, fibronectin and β_2 -glycoprotein I [15,20]. It is worth stressing that AECA are not specific to endothelial cells, as antigen determinants for them are also present on fibroblasts, leukocytes and blood monocytes [1].

The discussed antigens induce a proinflammatory and proadhesive endothelial cell phenotype through the NF- κ B activation pathway [24]. The AECA endothelial cell influence is associated with the concentration of these antibodies and causes the increases of functional monocyte adhesion, and the adhesion molecules expression such as E-selectin, intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule 1 (VCAM-1), as well as enhanced secretion of chemoattractant

proteins and cytokines such as monocyte chemoattractant protein-1 (MCP-1) and interleukin-1 (IL-1), interleukin-6 (IL-6) and interleukin-8 (IL-8), [15,20-22,25].

In SLE patients, AECA may bind the complement and most probably this mechanism also is involved in vasculitis, yet this is still under discussion [1,22]. Del Papa et al. [1] demonstrated that plasma from systemic vasculitis patients displayed AECA antibody-associated cytotoxicity, which occurs uniquely in the presence of lymphocytes. The monoclonal AECA cause increased IL-6 secretion, which may accelerate the lymphocyte infiltration rate, causing vascular damage [22].

The anti-endothelial cell antibodies of IgG class probably activate leukocytes which infiltrate the blood vessel wall. The *in vitro* experiments demonstrated enhanced leukocyte adhesion to human umbilical vein endothelial cell, depends on higher expression adhesion molecules [22]. This creates conditions for maintaining close cell contact with the vessel wall and for proinflammatory endothelial cell activation, manifested by adhesion molecule expression and increased cytokine secretion [22].

The AECA may induce endothelial cell apoptosis independently of Fc receptor [21,26]. The presumable AECA antigen determinant in the apoptosis process is heat shock protein (HSP) 60 [26]. A cross-reaction between AECA and Hsp60 has been demonstrated in SLE vasculitis patients [27].

It is believed that AECA take part in thrombus formation in SLE patients [28]. They may react with various components of endothelial cells and extracellular matrix, including proteoglycan molecules, bound with negatively charged glycosamino glycans (GAG), i.e. heparan sulfate and hyaluronate [28]. Direskeneli et al. [28] demonstrated that heparin inhibits the effect ascribed to AECA in a dose-dependent manner. The endothelial cell activation that is AECA dependent may induce prothrombotic lesions as a result of increased release of plasminogen activator inhibitor 1 (PAI-1), platelet activating factor [25] and thrombomodulin, together with enhanced von Willebrand factor synthesis [20,21]. It has been suggested that soluble thrombomodulin is a marker of endothelial damage in the microcirculation [29].

It is worth mentioning that the AECA probably take part in urticarial vasculitis with the C1q deficiency and the IgG anti-C1q antibody presence [1]. It is suggested that these antibodies may specifically induce clinical symptoms including angioedema, joint pain, eye inflammation, glomerulonephritis and chronic obstructive pulmonary disease [1].

In summary, although a potential role of the AECA in the vasculitis pathogenesis has not been fully determined yet, several lines of evidence have demonstrated that AECA is a factor that causes endothelial damage in SLE [1,15,20,22,24,28].

Antiphospholipid antibodies

It has been suggested that endothelial damage of whatever origin exposes endothelial cell phospholipids, which enables the adhesion of antibodies directed against phospholipids (aPL) [12].

These antibodies cause further vascular endothelial damage, an increased arterial and venous thrombosis risk and proliferative heart valve lesions [30]. It has been postulated that aPL antibodies perturb endothelial function, and promote thrombus formation during infection or pregnancy [18].

The antigen specificity of aPL antibodies includes the negatively charged cell membrane phospholipids, i.e. cardiolipin (CL), diphosphate glycerol, phosphatidyl ethanol amine, phosphatidyl ethanol serine [30]. Lysophosphatidylcholine (LPC) may also induce an immune reaction, leading to vascular inflammatory lesions, and other SLE symptoms [30]. In SLE patients, a clinical syndrome including the presence of aPL and vascular thrombi is now known as the secondary antiphospholipid syndrome [30]. It is worth mentioning that the β_2 -glycoprotein I, and other plasma proteins may change the phospholipid antigenicity through neoantigen formation [30].

The pathogenetic action mechanisms of aPL antibodies are variable. When binding with membrane phospholipids aPL antibodies may inhibit reactions catalyzed by them in the coagulation cascade, for example through inhibition of C and S protein activation [18]. These antibodies may also activate endothelial cells thrombin formation [18]. The binding of aPL antibodies with platelet membrane phospholipids binding protein predisposes to platelet activation and adhesion, with consequent thrombus formation [18]. These antibodies probably also participate in the complement system activation [18]. As a result, the aPL antibodies demonstrate proadhesive, proinflammatory and prothrombotic effects on endothelial cells [18]. The activity of aPL antibodies may also be linked to the development of early atherosclerosis in SLE patients [18].

Antineutrophil cytoplasmic autoantibodies

The antineutrophil cytoplasmic autoantibodies (ANCA) are directed against cytoplasmic antigens contained in azurophilic granules of neutrophils and monocyte lysosomes [2,31,32]. These antibodies belong to a heterogeneous family and are reported in all immunoglobulin classes [2,31,32]. According to indirect fluorescent labeling images, there are cytoplasmic (cANCA) and perinuclear ANCA (pANCA), and atypical cANCA and ANCA, forms [2,31-34]. The cANCA antibody activity is directed against the proteinase 3 (PR3), while pANCA antibodies activity is directed against myeloperoxidase (MPO). It should, however, be stressed that they react also with other proteins [2,33-35].

Initially, the ANCA presence was associated only with primary systemic vasculitis. A relation of cANCA (PR3-ANCA) with Wegeners granulomatosis, and that of pANCA (MPO-ANCA) with microscopic polyangiitis, and crescentic glomerulonephritis, has been demonstrated [31,32]. It is known however that ANCA antibodies occur also in secondary vasculitides associated with systemic connective tissue diseases, including SLE. In 15–20 % of SLE patients, ANCA antibodies, usually pANCA, have been reported [2].

Vasculitis in SLE patients is a well documented phenomenon; however, the ANCA antibodies role in the inflammation pathogenesis is still under discussion [2]. The relation between the pANCA titer and SLE activity has not been confirmed yet, in particular that the relation between the mentioned antibodies presence and SLE specific organ complications has not been demonstrated [31]. Therefore, conclusions from available studies remain ambiguous [31].

The antineutrophil cytoplasmic autoantibodies associated vasculitis is characterized by the occurrence of focal necrotic foci of capillaries, venules and sometimes arterioles [36]. It is suggested that necrosis development may be the result of microcirculation sequestration of activated neutrophils and monocytes [36,37]. Various cytokines, chemokines, bacterial lipopolysaccharides and intestinal toxins activated cells are to increase the azurophilic granules membrane expression, which contain the ANCA specific antigens, PR3 or MPO [36]. At this stage ANCA by binding and forming immune complexes with PR3 or MPO would be to activate neutrophil adhesion to endothelial cells, with consequent extravascular permeation, vessel damage and apoptosis development [2,32,37]. A direct involvement of integrin and cytokine receptors, and a protective effect of β_2 -integrin antibodies in endothelial damage have been demonstrated [37]. It has also been shown that the IgG, PR3-ANCA antibodies stimulate neutrophil degranulation and lysosome enzyme release, highly reactive forms of oxygen and nitric oxide [2,36]. These forms and lysosome enzymes most probably cause damage to the vascular basement membrane [36]. The released PR3, taking part in proteoglikan and elastin degradation, would be to cause damage of endothelial cells and induce apoptosis in them [36]. The activating effect of PR3 and MPO on T helper CD4 lymphocytes proliferation, has also been postulated [2]. Most probably ANCA also take part in inflammation, inhibiting PR3 binding with the α_1 -antitrypsin inhibitor and, as a result, decreasing the antigen and immune complexes decomposition [2]. The ANCA role in systemic vasculitis in SLE patients, so far remains unclear.

Anti-double-stranded DNA antibodies

Anti-double-stranded DNA antibodies (anti-dsDNA) antibodies may take part in vascular damage in SLE. They possess an anti-endothelial activity, which is directed against certain antigens on endothelial surface [22]. Their direct cytotoxic effect on endothelial cells has not, however, been demonstrated [1]. The synthesis of IL-1 and IL-6 induced by the anti-dsDNA antibodies has only been demonstrated, which can indirectly indicate endothelial cell activation [20]. The anti DNA-histone complexes antibodies have a similar effect [22]. Additionally, circulating DNA fragments contribute to SLE vasculitis pathogenesis [38]. The endothelial cells ICAM-1 expression stimulation, and the mRNA IL-6, IL-8, TNF- α , IFN- γ synthesis increase, with participation of DNA fragments, has been shown [38].

Cellular adhesion molecules

Cellular adhesion molecules enable the leukocyte adhesion and rolling along the endothelial cells surface, and control leukocyte permeation to inflammation affected tissues [29,39]. Enhancement of granulocyte cell surface, and endothelial, adhesion molecules expression, determines the adhesion of these molecules to the vascular wall and their secondary permeation to extravascular space [39]. The adhesion molecules are also a molecular signal for the immune memory lymphocytes towards a certain antigen and enable a constant lymphocyte flow through tissues, where a certain antigen has been discovered for the first time [29].

Cellular adhesion molecules are classified to 3 groups, i.e. selectins, integrins and immunoglobulin superfamily (IGSF) [29].

E-Selectin expression is limited to activated endothelial cells. E-Selectin influences the initial adhesion of nonactivated leukocytes (neutrophils, monocytes and immune memory T lymphocytes) to activated endothelial cells and enables leukocyte rolling and possibly plays the role of an intracellular transmitter [39]. E-selectin expression is stimulated by IL-1 and TNF- α [29]. E-selectin is the specific inflammatory marker, of endothelial cell activation [40].

The leukocyte surface integrins are the Lymphocyte function-associated antigen-1 (LFA-1), and very late antigen-4 (VLA-4) [29]. The integrins bind with the IGSF group receptor, which contains adhesion molecules, ICAM-1 and VCAM-1 [29]. The expression of both adhesion molecules on the endothelium surface requires inflammatory cytokine induction, TNF- α , IL-1 and IFN- γ [29]. The adhesion molecule VCAM-1 reacts with cells with the VLA-4 chain expression in monocytes, lymphocytes, macrophages, glomerular parietal epithelial cells, basophils and eosinophils [39].

In SLE associated necrotizing vasculitis there is increased VLA-4 expression, which binds with the fibronectin CS-1 domain [41]. This process enables T lymphocyte-activated endothelial cell adhesion [41].

The role of cellular adhesion molecules in SLE vasculitis

In SLE patients there are alterations in cellular adhesion molecule expression [29]. Predominant adhesion molecules locally participating in SLE inflammation formation are most probably E-selectin, ICAM-1 and VCAM-1 with their ligands, i.e. Sialyl Lewis X (sLeX), LFA-1 and VLA-4 [29]. It has been demonstrated that LFA-1 expression on peripheral blood lymphocytes is increased in the SLE patient group [29]. Increased levels of LFA-1 and VLA-4 in vasculitis patients have also been reported [29]. The anti-dsDNA and class IgG ACEA antibodies have been reported to increase expression of cellular adhesion molecules [39]. Antibodies and immune complexes created with their participation induce the cytokine synthesis and increase the endothelial cells adhesion molecules expres-

sion, with a resulting granulocyte aggregation secondary effect [39]. The induction of ICAM-1 and VCAM-1 expression in HUVEC with the use of purified IgG from SLE patients, has been demonstrated [29]. A closer endothelial cell lymphocyte adhesion in active SLE patients, has not, however, been demonstrated, and results of studies dealing with this issue were contradictory [29]. Moreover, T lymphocytes of patients with active SLE and accompanying lymphopenia were characterized by the IL-1 stimulated decreased adhesion potency to HUVEC [29]. It is postulated that cells of potent adherence may be eliminated from the blood stream, which could explain the lymphocyte count decrease in active SLE [29].

Soluble forms of adhesion molecules

Increased levels of soluble forms of adhesion molecules and IL-6 are reported in plasma of SLE patients, indirectly indicating endothelial cells activation [22]. These molecules are enzymatically released from the cytokine-activated cell surface [29,39]. Several studies demonstrated a correlation between their levels and the disease activity [29,39]. In the SLE patients, plasma sVCAM-1, soluble E-selectin and sICAM-1 levels are increased [39]. It has been shown that sVCAM-1 levels correlated with SLE activity [39]. The sVCAM-1 serum levels were increased in the active forms of lupus nephritis such as in neuropsychiatric SLE and deep vein thrombosis associated with antiphospholipid syndrome in SLE patients [29]. The sVCAM-1 titer correlated with severe thrombotic complications and thrombotic microangiopathy with renal failure [29]. It has also been demonstrated that the levels of all soluble adhesion molecules such as sVCAM-1, sICAM-1 and sE-selectin, correlated with the aPL titer [29]. A relation between sVCAM-1 and soluble trombosmodulin has been demonstrated [29]. The sE-selectin and sICAM-1 increase in SLE vasculitis, however, is believed to be a multiorgan damage marker [40]. There are suggestions that soluble adhesion molecules may play a protective role in SLE. It has been postulated that the soluble E-selectin may protect against lupus nephritis development [29]. Several authors suggest that it could exert physiological effects by influencing interactions between endothelial cells and circulating leukocytes; other studies, however, demonstrated that sE-selectin is rather a inactive decomposition product [29]. Similar findings refer to the role of sP-selectin [29].

Pentraxin 3

Pentraxin 3 (PTX3) is believed to be the small vessel vasculitis activity indicator [42]. Moreover, its level increases in the early stages of irreversible muscle cell damage [42]. Pentraxins take part in the regulation of the remaining cells removal [42]. It has recently been demonstrated that PTX3 prevents the apoptotic cells internalization to monocytes [42].

The cells producing PTX3 have been identified in the skin [42]. The synthesis of the co-called long PTX3 increases in endothelial cells as a result of the IL-1 gene induction and

in fibroblasts as a result of TNF- α induction. Both cell types play an important role in the pathogenesis of systemic vasculitis. Moreover, proinflammatory triggers induce PTX3 expression in monocytes, macrophages and in the endothelium [42].

Drug-induced vasculitis in SLE

Some drugs may play a role in the induction of inflammatory vascular lesions in SLE. The drug molecule may act as a hapten, which as a result of autoantigen binding alters the antigen properties. Several SLE inducing drugs are listed below: penicillins, allopurinol, thiazides, pyrazolones, retinoids, streptokinase, cytokines, monoclonal antibodies, chinolons, hydantoin, carbamazepine and other anticonvulsants [1].

Infection-induced SLE vasculitis

Vasculitis may be a result of direct attack of microorganisms on the blood vessel wall or may be caused by infected thrombotic mass [11].

Hepatitis C virus may take part in vasculitis development, with the cryoglobulin presence [1,14]. This factor participation should be considered in SLE patients with large blood vessel inflammation of the lower extremities [1]. There is an unexplained relationship between blood cryoglobulins and hepatitis C [11]. The following mechanisms leading to viral and bacterial vasculitis in SLE have been suggested:

- 1) the viruses directly attack the vascular wall inducing an inflammatory process
- 2) some of them, as cytomegalovirus, may permeate and activate endothelial cells leading to vasculitis
- 3) bacterial *Staphylococcus* antigens, as for example neutral phosphatase, may bind with basement membranes and adhere specifically to IgG, which in turn induces an immune response and an inflammatory process [11].

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