Netherlands
The Journal of Medicine

REVIEW

Vascular manifestations of systemic lupus erythematosis

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ABSTRACT

Systemic lupus erythematosus (SLE) is an autoimmune connective disease, where vascular lesions are one of the typical symptoms. The differentiation of the type of vascular complications in SLE is very difficult, sometimes impossible, and requires an in-depth immune and histopathological approach, and extensive clinical experience. It may play a key role in the choice of treatment strategy and prediction of patient prognosis. SLE is a prototype of a multisystem autoimmune connective tissue disease, marked by immune complex-mediated lesions of blood vessels in diverse organs. Therefore, awareness of the aetiology, pathophysiology, the clinical and histopathogical setting, and SLE-associated vascular complications is of great clinical significance. In this review, the spectrum of vascular abnormalities and the options currently available to treat the vascular manifestations of SLE are discussed.

KEYWORDS

Systemic lupus erythematosus, vasculitis, vasculopathy, antiphospholipid syndrome

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease with heterogeneous manifestations, including internal organ damage, which can result in severe morbidity and even death and often requires aggressive immunosuppressive treatment. SLE is a connective tissue autoimmune disease, where vasculopathy is one of the most typical symptoms.[1] Vascular involvement is frequent in SLE patients and represents the most frequent cause of death in established disease. In this context, vasculopathy can be directly aetiologically implicated in the pathogenesis of the disease, presenting as an acute/subacute manifestation of lupus (e.g., antiphospholipid syndrome (APS), lupus vasculitis). Besides overt vessel obstruction, vascular disease in lupus, especially when affecting medium- and small-sized vessels, may contain both vasculopathic and vasculitic pathophysiological parameters.

Livedoid vasculopathy, a condition which can be observed in patients with SLE/APS or specific forms of systemic vasculitis (mainly polyarteritis nodosa and cryoglobulinaemia) is associated with chronic ulcerations of the lower extremities and characterised by uneven perfusion.[2] The pathogenesis of livedoid vasculopathy has not been fully elucidated, or rather, cannot be solely attributed to a particular mechanism, as both hypercoagulable states, as well as autoimmune diseases, appear to associate with and contribute to its development.[3]

The typical histological findings show dermal blood vessel occlusion.[4] The histopathological findings of intravascular fibrin, segmental hyalinisation, and endothelial proliferation clearly support the thrombotic parameter of its pathogenesis.[5] The presence of immunoreactants in the vessel wall and circulating immune complexes (such as rheumatoid factor) are in favour of its immunological component; the absence, however, of fibrinoid necrosis and inflammatory infiltration of the vessel wall differentiates livedoid vasculopathy from true vasculitides.

It is reported in 10-40% of patients, occurs more often in women (80%) than in men and may precede the development of a full-blown SLE.[6] Vascular lesions in SLE are commonly known as lupus vasculopathy; a typical lupus vasculitis with inflammatory and vascular wall necrosis and a thrombus in the lumen of the affected artery occurs less often.[7-9] However, the rate of thrombotic

events is higher in patients with disease of recent onset, when compared with patients with other autoimmune diseases and remains so throughout the course of the disease;[10] in the LUMINA study, which included multiethnic SLE patients of recent diagnosis, age, damage accrual at enrolment, and antiphospholipid antibodies as well as the use of higher dosages of glucocorticoids were associated with a shorter time interval to thrombotic events.[11] Appel *et al.*[8] provided an SLE vasculopathy classification including: non-complicated vascular deposits of immune complexes, non-inflammatory necrotic vasculopathy, thrombotic microangiopathy and true lupus vasculitis. Of all lupus vasculitis cases more than 60% involve leucocytoclastic inflammation, 30% are vasculitis with cryoglobulinaemia, and systemic vasculitis resembling polyarteritis nodosa constitutes about 6% of SLE vasculitides patients.[8,12-14] 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.[8] SLE-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 the development of organ complications, and vasculitis within the internal organs.[15,16] Lupus vasculitis is usually seen in cutaneous vessels, in renal glomeruli, coronary and brain vessels, the brain, lung alveoli and less often in the gastrointestinal tract.[1] In SLE, small-vessel vasculitis with necrosis of vascular walls has been found in lymph nodes.[17] Nevertheless, due to local deposition of immune complexes in the blood vessels, vasculitis may play an important role in the pathogenesis of necrosis in lupus lymphadenitis. These disorders closely mimic malignant lymphomas both clinically and pathologically; therefore it is necessary to do extensive clinical evaluation.[18]

It has to be stressed that cutaneous lupus vasculopathy is the most common manifestation of SLE, and is reported in 94% of patients with lupus vasculitis.[19,20] Mild forms are characterised by purpura, urticaria lesions or bullous lesions of extremities, and livedo reticularis on the trunk. It has been demonstrated that internal organ vessels are affected in 18% of SLE vasculitis patients. 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 haemorrhage.[1] Brain vasculitis only occurs in about 10% of SLE patients and associated clinical symptoms are very variable: from mild cognitive dysfunction to severe psychosis and convulsions, local ischaemia and strokes.[1,21] 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 haemorrhage or perforation.[1]

ANTIPHOSPHOLIPID SYNDROME

The clinical APS, an autoimmune syndrome usually developing in the context of SLE, is a condition defined as a predisposition for arterial and/or venous thromboses and/or recurrent miscarriages or other obstetric emergencies (e.g., premature birth, preeclampsia) in association with haematological abnormalities and specific antibodies targeted against phospholipid-binding plasma proteins.[22] The most severe form of APS is catastrophic APS, which is characterised by widespread small-vessel thrombosis with multiorgan failure and more than 50% mortality.[23] It has been suggested that endothelial damage of whatever origin exposes endothelial cell phospholipids, which enables the adhesion of aPL antibodies.[19] In 1998, the preliminary classification criteria for APS were proposed at Sapporo, Japan.[24] Classification for this syndrome needed at least one clinical manifestation together with positive tests for circulating antiphospholipid (aPL) antibodies, including lupus anticoagulant or anticardiolipin, or both, at medium-high values, detected at least twice in six weeks. In 2006, classification criteria were updated (*table 1*).[25] Essentially, the clinical criteria remained unchanged,

Table 1. *Classification criteria for antiphospholipid syndrome*

Clinical criteria	
Vascular thrombosis	One or more clinical episodes of arterial, venous or small-vessel thrombosis in any tissue or organ, confirmed by objective criteria. Histopathology should show thrombosis without significant inflammation in the vessel wall
Pregnancy morbidity	One or more unexplained deaths of a morphologically normal foetus at or beyond 10 weeks' gestation OR One or more premature births of morphologically normal neonate at or before 34 weeks' gestation due to pre-eclampsia or placental insufficiency OR Three or more unexplained, consecutive, spontaneous abortions before 10 weeks gestation, excluding maternal anatomical or hormonal abnormalities, and excluding maternal and paternal chromosomal causes
Laboratory criteria	Medium/high titre IgG and/or IgM isotype anticardiolipin antibody in blood on 2 or more occasions at least 12 weeks apart using standard assays Lupus anticoagulant present in plasma on two or more occasions at least 12 weeks apart Anti-β_2 glycoprotein-I IgG or IgM in blood on two or more occasions at least 12 weeks apart using standard assays.

however, two important modifications were made: the time elapsed between two positive determinations was extended to 12 weeks to assure the detection of persistent antibodies only; and anti-β2-glycoprotein I, both IgG and IgM, were added to the laboratory criteria. Notably, IgA isotypes, antiprothrombin antibodies, and antibodies directed against phosphatidylserine-prothrombin complex remained excluded from the criteria. During the last few years these modifications have been criticised, and the debate about the clinical implications of different antiphospholipid antibodies is still open.[26] Recent clinical studies have confirmed lupus anticoagulant as consistently the most powerful predictor of thrombosis.[27-29]

The pathogenetic action mechanisms of aPL antibodies are variable. When binding with membrane phospholipids aPL antibodies may inhibit reactions catalysed by them in the coagulation cascade, for example through inhibition of C and S protein activation.[30] These antibodies may also activate endothelial cell-mediated thrombin formation.[30] The binding of aPL antibodies with platelet membrane phospholipids binding protein predisposes to platelet activation and adhesion, with consequent thrombus formation. These antibodies probably also participate in complement system activation.[30] As a result, the aPL antibodies demonstrate proadhesive, proinflammatory and prothrombotic effects on endothelial cells.[30] Thrombosis within the context of APS may occur even in histologically normal vessels. However, in the majority of aPL-positive patients, seropositivity *per se* does not suffice for the development of clinical events. Thrombotic events seem to occur more readily in SLE patients with coexistent atherosclerosis.[31] Recently, the presence of microangiopathy, defined as capillary micro-haemorrhages, and diagnosed with the aid of capillaroscopy, has been proposed as an augmentary screening tool for aPL-seropositive patients who are prone to develop clinical thrombotic manifestations.[32]

Optimal treatment of APS patients is still controversial and is continually under review due to the small number of adequate clinical prospective studies. Treatment of APS patients must be based on the use of platelet antiaggregating agents or anticoagulants. In asymptomatic patients with elevated titres of aPL antibodies, additional vascular risk factors such as hypertension, hypercholesterolaemia, tobacco use or oral contraception containing oestrogen have to be addressed and treated.[33] In view of its low potential for toxic effects, many experts understandably recommend low-dose aspirin (combined with hydroxychloroquine) to be considered as primary thromboprophylaxis in SLE patients with lupus anticoagulant or persistently positive anticardiolipin, or both.[34]

APS patients who present with thrombosis have an elevated risk of suffering new thrombotic phenomena; the main treatment for that group of patients is antithrombotic treatment, rather than immunosuppression.[35] The present state of knowledge recommends treatment with oral anticoagulants for an indefinite amount of time and maintaining an international normalised ratio (INR) between 2 and 3 for APS patients with venous and arterial non-cerebral events.[36,37] Some studies have suggested that in APS patients with arterial thrombosis more aggressive treatment is needed with a target INR of more than 3 (INR 3-4).[38-40] Heparin and low-dose aspirin are the treatments of choice for APS in pregnancy. Neither conventional heparin nor low-molecular-weight heparin cross the placenta and, therefore, do not affect foetal development. Prolonged use of fractioned heparin has been associated with the development of maternal osteoporosis. Low-molecular-weight heparin is being used to treat these patients and seems to have the least effects on bone mass.[41] Heparin must be maintained throughout pregnancy and the postpartum period until the patient restarts oral anticoagulation. Thrombocytopenia associated with the presence of aPL antibodies is usually moderate and does not require treatment. Nevertheless, in the case of severe thrombocytopenia (less than $50 \times 10^9/\mu l$) treatment with corticosteroids, intravenous immunoglobulins or some immunosuppression drugs is usually effective.[42] B-cell depletion therapy with anti-CD20 (rituximab) monoclonal antibodies has been used recently in the treatment of severe thrombocytopenia.[43] The treatment of the catastrophic form of APS is the greatest challenge. Less severe cases can be managed with anticoagulation and high-dose steroids. However, in the case of life-threatening manifestations, either intravenous immunoglobulins or plasma exchange should be added.[44] There is not the same degree of agreement of intensity and duration of anticoagulation but we recommend it for the lifetime. Recommendations for APS treatment are summarised in *table 2*.

LUPUS VASCULITIS

Distinction of inflammatory lupus vasculitis from APS, which may present with similar clinical manifestations, is of major significance in terms of clinical management. Inflammatory vascular disease is triggered by the in situ formation, or the deposition, of immune complexes within the vessel wall.

Vasculitis is an inflammation of vessel walls.[45] This vascular inflammatory process may take many clinical forms due to its capacity to affect vessels of different sizes (arteries, veins, and/or capillaries) and sites (involving either skin or internal organs), with a prognosis that may range from mild to life-threatening.[1,46] Current classification schemes recognise approximately 20 primary forms of vasculitis, with the most valid basis for classifying

Table 2. *The treatment of antiphospholipid syndrome*

Clinical situation		Treatment
Asymptomatic		Strict control of vascular risk factors: - smoking - hypertension - hypercholesterolaemia - oral contraception
		Observation and/or low-dose aspirin (75 to 150 mg)
		Hydroxicloroquine/cloroquine
Thrombosis	Deep venous – 1st event	Lifelong oral anticoagulant (INR 2-3)
	1st stroke	Lifelong oral anticoagulant (INR 2-3) and/or low-dose aspirin
	Transient ischaemia	Low-dose aspirin
	1st non-cerebral arterial event	Lifelong oral anticoagulant (INR 2-3) and low-dose aspirin
	Recurrent arterial/venous event	Indefinite amount of time / lifelong oral anticoagulant (INR 3-4) or LMWH
	Catastrophic APS	IV heparin IV high-dose steroids Plasma exchange or IVIG
Pregnancy	No previous history	Observation and/or low-dose aspirin
	Recurrent first trimester or second/third trimester foetal loss	LMWH and low-dose aspirin
Thrombocytopenia	Mild (100-150)	Observe
	Moderate (50-100)	Observe
	Severe (<50)	High-dose steroids, IVIG, rituximab

INR = international normalised ratio; LMWH = low-molecular-weight heparin; IVIG = intravenous immunoglobulins.

the vasculitides being the size of the predominant blood vessels involved (large, medium-sized, or small-vessel vasculitis).[47] However, in recent years there has been growing interest in classifying the clinical vasculitic syndromes into primary and secondary forms.[48] In the primary group, the primary pathology involves the blood vessels. In the secondary group, inflammation of blood vessels occurs as a complication of the underlying disease process (mainly systemic autoimmune diseases) or is triggered by exogenous factors such as drugs, infections, or neoplastic manifestations.

Whereas cutaneous vasculitis is the most common form of SLE vasculitis, visceral involvement is described in less than 10% of cases but can be life-threatening and require aggressive treatment.[49] SLE cutaneous vasculitis is presented by a wide spectrum of lupus nonspecific lesions, such as purpural, urticarial, and limb lesions, which can be both lymphocytic or leukocytoclastic infiltration types.[50] Visceral vasculitis in SLE mostly coincides with systemic flares and is frequently reported to occur following or in association with cutaneous vasculitis. Common types of SLE vasculitis are shown in *table 3*.

Vasculitis may manifest in as many as 56% of SLE patients throughout their life, in contrast to antiphospholipid syndrome which has a prevalence of 15%. Patients with vasculitis are mainly male and tend to be of younger age.[51] Antibodies against endothelial cells have been identified as a major endothelial cell cytotoxic effector and have been implicated in the pathogenesis of several

Table 3. *Common types of cutaneous and visceral vasculitis in SLE patients*

Cutaneous vasculitis	
	Punctate vasculitic lesions
	Palpable purpura
	Urticarial vasculitis
	Plaques and panniculitis
Visceral vasculitis	
	Central nervous system
	Peripheral nervous system
	Pulmonary vasculitis
	Gastrointestinal vasculitis
	Renal vasculitis
	Cardiac vasculitis
	Large vessel vasculitis

connective tissue diseases, predominantly vasculitides.[52] More than 80% of systemic lupus erythematosus patients are positive for antiendothelial cell antibodies (AECAs).[53] Other forms of SLE-related vasculitis include drug-induced vasculitis[54] and infection-induced vasculitis[55] either through direct compromise of the vascular wall by pathogens, or through antigen-induced autoimmune and inflammatory processes. 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. Some of the SLE-inducing drugs are: penicillins, allopurinol, thiazides, pyrazolones, retinoids, streptokinase,

cytokines, monoclonal antibodies, chinolons, hydantoin, carbamazepine and other anticonvulsants.[1,56] Vasculitis may be a result of a direct attack of microorganisms on the blood vessel wall or may be caused by infected thrombotic mass.[16] Hepatitis C virus may take part in vasculitis development, with the cryoglobulin presence.[57] There is an unexplained relationship between blood cryoglobulins and hepatitis C.[16] 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 and 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.

Vasculitis is among the most characteristic processes involved in the cutaneous and visceral expression of SLE. The development of vasculitis in SLE is of prognostic value. Reduction of SLE activity and prevention of flares (which are partly due to vasculitis) is the key point of treatment. Cutaneous SLE vasculitis is successfully treated with antimalarial agents. The discontinuation of antimalarial agents is clearly associated with an increased risk of both skin vasculitis and systemic SLE flares.[58] Thalidomide was reported to improve cutaneous lupus erythematosus, especially when antimalarial agents were unsuccessful in achieving remission of cutaneous lupus erythematosus or cutaneous vasculitis.[59] Dapsone, known for its antimicrobial properties, is also an immunomodulatory agent that is effective in the treatment of cutaneous vasculitis in SLE.[60] SLE is generally treated with glucocorticoids in combination with some steroid-sparing agents. In the treatment of visceral forms of SLE vasculitis cyclophosphamide and azathioprine are the two most commonly used cytotoxic immunosuppressive agents.[61] If there is major organ involvement, these medications, in combination with corticosteroids, need to be employed early in order to prevent or minimise irreversible damage. Many studies have shown the benefit of intravenous immunoglobulin in suppressing SLE flares and controlling and treating visceral vasculitis.[62] Recently mycophenolate mofetil has been introduced in the treatment of SLE and seems to be effective in controlling global disease activity even when other therapeutic regimens have failed.[63] However, few studies on the use of mycophenolate mofetil in the treatment of refractory cutaneous lupus erythematosus are available and their results are controversial.[64] Based on knowledge of the different dysregulated immunological pathways involved in SLE pathogenesis, specific targeted therapies have been developed. Rituximab is currently not an approved agent for the treatment of SLE. Nevertheless, in refractory SLE patients the addition of rituximab to the immunosuppressive treatment (as an off-label drug) may be considered.[65] Belimumab is a human monoclonal antibody that inhibits B-cell activating factor (BAFF), also known as B-lymphocyte stimulator (BLyS) and it is approved for the treatment of mild-to-moderate SLE.[66,67]. Belimumab should be considered in SLE patients with visceral vasculitis who are refractory to various combinations of immunosuppressives/immunomodulators agents.

CONCLUSION

Vascular involvement in SLE, either as a direct complication of the disease or developing as an accompanying comorbidity, significantly impairs the quality of life of SLE patients and represents the most frequent cause of death.[68] Vascular involvement in SLE 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 disease pathogenesis.[1,69] It seems that endothelial cell activation with pronounced expression and activation of adhesive molecules are the key factors in the pathogenesis of this disease.[19,69] Activated endothelial cells are able to bind various proteins and cells to the vessel wall. This process is at first limited only to postcapillary venules, which are often affected in the small vessel disease. However, vasculitis localisation in arterial branching is most probably the result of compression forces.[19] The damage localisation may also depend upon the hydrostatic pressure values and local blood circulation disorders.

Understanding of the vascular abnormalities and the underlying pathogenic process is clearly important for providing new insights into the treatment of SLE. Continued research into the mechanisms of lupus-related vascular involvement will hopefully provide effective tools and targets to improve their survival and overall quality of life.

CONFLICT OF INTEREST

None

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