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VASCULITIS (L ESPINOZA, SECTION EDITOR)

Vasculitis in Systemic Lupus Erythematosus

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Abstract Systemic lupus erythematosus (SLE) is a complex heterogeneous autoimmune disease with a wide variety of clinical and serological manifestations that may affect any organ. Vasculitis prevalence in SLE is reported to be between 11 % and 36 %. A diverse clinical spectrum, due to inflammatory involvement of vessels of all sizes, is present. Even though cutaneous lesions, representing small vessel involvement, are the most frequent, medium and large vessel vasculitis may present with visceral affection, with life-threatening manifestations such as mesenteric vasculitis, pulmonary hemorrhage, or mononeuritis multiplex, with detrimental consequences. Early recognition and an appropriate treatment are crucial. Recent studies have shown that vasculitis in patients with SLE may present different clinical forms based on the organ involved and the size of the affected vessel. It is noteworthy that the episodes of vasculitis are not always accompanied by high disease activity. Recent articles on this topic have focused on new treatments for the control of vascular disease, such as biological therapies such as Rituximab and Belimumab, among others.

This article is part of the Topical Collection on *Vasculitis*

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Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disease with a wide variety of clinical and serological manifestations that may affect any organ. Vasculitis, characterized by the presence of inflammatory cell infiltration and subsequent necrosis of blood vessel walls, is among the most characteristic processes involved in the clinical evolution toward SLE [1] and is considered among the leading causes of death in people with established disease [2••]. This vascular inflammatory process may take many clinical forms dependent on the size of the affected vessels (arteries, veins, and/or capillaries) and the sites involved (skin or internal organs), with a prognosis that may range from mild to life-threatening.

Most studies analyzing the prevalence of vasculitis in large series of SLE patients show a prevalence ranging between 11 % and 36 %. Episodes of vasculitis often occur during a "lupus flare," with constitutional symptoms such as fever, fatigue, and weight loss; a higher prevalence of livedo reticularis, anemia, elevated erythrocyte sedimentation rate, and anti-La/SS-B has been reported as well [3, 4].

Vascular inflammation may occur by deposition of immune complexes in the vascular path, which shows affected segments interspersed with normal areas. The presence of anti–endothelial-cell antibodies, which cause cell destruction, has also been observed [5]. The presence of these autoantibodies has been documented in 80 % of patients with SLE [6]. Apparently, such autoantibodies may bind to antigens such as histones, DNA, ribosomes, adenylyl-cyclase-associated protein, profilin II, fibronectin, and b2-glycoprotein. When fixing antibodies, the monocyte inflammatory response, by attracting and releasing cytokines, leads to an increase in local

inflammation within the vascular endothelium [7]. Other types of autoantibodies that may be involved in the pathophysiology of lupus vasculitis are neutrophil cytoplasmic antibodies, which have been observed as a fundamental part of primary vasculitis and may be positive in 20 % of SLE patients [8].

In the two largest studies of vasculitis in SLE, Drenkard et al. observed, in a cohort of 540 SLE patients, incident vasculitis in 194 during a follow-up period of 10 years. Cutaneous involvement was reported in 160 patients (82.4 %), visceral in 24 (12.3 %), and both in 10 (5.1 %). This case–control study showed that patients with vasculitis had longer disease duration, had younger age of onset, and were more frequently males [3].

Ramos-Casals et al. conducted a cohort study in Barcelona between 1980 and 2004, with the finding of 76 out of 540 patients (11 %) developing vasculitis. Cutaneous lesions were the main clinical presentation in 68 (89 %) patients, while the remaining 8 (11 %) had isolated visceral vasculitis; 65 (86 %) patients had small vessel vasculitis (SVV), and 11 (14 %) had medium-sized vessel vasculitis (MVV). A higher prevalence of mononeuritis multiplex, visceral vasculitis, and ulcerated/ischemic cutaneous lesions was observed, as well as a higher percentage of surgical interventions in patients with MVV, as compared with patients with SVV [4].

Although vasculitis is a characteristic process involved in the systemic expression of SLE, few studies have analyzed the clinical features of vasculitis in patients with SLE. Due to the limited information and the need for up-to-date evidence, the recent literature on the topic is summarized in this review.

Skin Vasculitis

Cutaneous vasculitis was found in 19 %–28 % in a descriptive analysis of 704 European lupus patients [9]. Vasculitic lesions in SLE include palpable purpura, petechiae, papulonodular lesions, livedo reticularis, cutaneous infartaction, erythematous plaques, erythema with necrosis, panniculitis, splinter hemorrhages, and superficial ulcerations.

In at least two large cohort studies in patients with vasculitis and SLE, the most frequent type of vasculitis was SVV, defined as leucocytoclastic vasculitis, which may be limited to the skin but also tends to affect renal glomerular capillaries and pulmonary interalveolar septae, manifesting as haematuria and haemoptysis, respectively [3, 4]. Most patients present cutaneous features consisting of erythematous or violaceous punctuate lesions on the fingertips and/or palms, which are nonblanching with pressure. The histological presentation is a severe pandermal vasculitis often accompanied by thrombosis, with resultant cutaneaous infarction [10]. Erythema elevatum diutinum is a rare chronic fibrosing form of leucocytoclastic vasculitis characterized by symmetric papules or nodules on the extensor surface of the extremities. It has been associated with hematological disorders and chronic infections, and there are a few case reports in patients with SLE [11].

Although urticarial vasculitis is a distinctive clinicopathological entity, it is considered a nonspecific finding that occasionally accompanies SLE. Hypocomplementemia is present in about one fifth of patients, half of whom have SLE. It is characterized clinically by urticarial lesions, which persist for longer than 24 h and leave a hypopigmented residuum. Histologically, there is erythrocyte extravasation, slight leucocytoclasia, and neutrophilic infiltration of vessel walls, with minimal fibrin deposition [10, 12].

The other main vasculitis reaction pattern is a lymphocytic vasculitis, which may be associated with concomitant cryofibrinogenemia and/or antiphospholipid antibodies.

Digital infarcts suggest vasculitis unless they are a consequence of Raynaud's phenomenon, although vasculitis may contribute to vaspoespasm [10].

Livedo reticularis is a clinical sign of disordered skin circulation as a resultant of multiple causes. Vasculitis is suggested if the condition is associated with tender subcutaneous nodules and suggests involvement of subcutaneous muscular arteries [12].

Gastrointestinal Vasculitis

Mesenteric Vasculitis (Lupus Enteritis)

Mesenteric vasculitis is one of the most devastating complications of SLE, with an estimated prevalence from 0.2 % to 9.7 % among all SLE patients and from 29 % to 65 % in patients whose presentation includes abdominal pain [13]. Bowel ischemia secondary to lupus mesenteric vasculitis (LMV) can lead to perforation and hemorrhage and has a high mortality of up to 50 %. It usually occurs in patients with active disease (SLEDAI <5) [14] and is frequently associated with thrombocytopenia, lymphopenia, central nervous system involvement, and cutaneous vasculitis [15•]; however, there are a few case reports (<1 %) with a low SLEDAI and leukopenia and in which antiphosholipid, as well as other autoantibodies, do not correlate with its occurrence [16].

LMV preferentially affects the superior mesenteric artery supply; the ileum and jejunum are most frequently affected (80 %–85 %), and the rectum less often (14 %) [3, 17]. Clinical symptoms include diffuse abdominal pain, nausea, bloodstained stool, and vomiting. On physical examination, bowel sounds are reduced or absent, and the abdomen may be distended and with diffuse tenderness and/or rebound tenderness [18]. Nevertheless, clinical symptoms, laboratory findings, plain radiography, and contrast studies are of limited value in the diagnosis, and bowel specimens from affected patients are not always available. Advances in the application

of computed tomography (CT) seem to compensate for this lack of pathological information. Common findings include dilated bowel, focal or diffuse bowel wall thickening, abnormal bowel wall enhancement (target sign), engorgement of mesenteric vessels (comb sign), and ascites. The treatment of choice is high-dose intravenous infusions of methylprednisolone or an equivalent agent, followed by a gradual tapering to a maintenance dose or to cessation of the medication. In severe cases of intestinal vasculitis, cyclophospamide is initiated at a dose of 1 mg/kg daily, and after stabilization is achieved, monthly pulse therapy is in order. Global assessment of SLE disease activity and early laparotomy (within 24–48 h) might improve the prognosis of patients with SLE who have abdominal pain. Medina et al. observed that none of the 33 patients (with either active or inactive SLE) who were operated on within 24–48 hdied, whereas 10 of 11 patients who underwent surgery after 48 h died [14].

Hepatic Vasculitis

Conflicting data on the incidence of hepatic vasculitis in SLE exist. Hepatic arteritis was found in 11 out of 52 cases (21 %), with pathologically proven liver diseases in SLE from the Japanese autopsy registry, in contrast with the report of the 33 histologically proven liver diseases in SLE by Runyon et al., in which none had vasculitis [19, 20]. Recently, a case report of hepatic vasculitis mimicking liver abcesses was published; this patient had negative cultures and resolution of the lesions by image, along with clinical improvement with steroid therapy [21]. Spontaneous rupture of the liver due to hepatic vasculitis accompanying arteritis of the pancreas, adrenal gland, and spleen has been reported by Levin et al. [22].

Pancreatic Vasculitis

Pascual-Ramos and coworkers reported pancreatitis in 35 of 895 SLE patients over a period of 17 years, an annual incidence of 2.3/1,000 [23]. The pathogenic mechanism responsible for pancreatic damage in SLE remains unknown, but vascular damage has been stressed. This includes necrotizing vasculitis syndrome, occlusion of arteries and arterioles by thrombi as a result of hypotension or antiphospholipid antibodies syndrome, intimal proliferation, and immune complex deposition with complement activation in the wall of pancreatic arteries. Although SLE-associated acute pancreatitis is uncommon, due to its potentially fatal outcome (18 %–27 % mortality), it should be suspected in any SLE patient with abdominal pain [24].

Coronary Vasculitis

At the cardiac level, coronary heart disease is common in patients with SLE, with a high prevalence of myocardial infarction in all age groups (up to 50-fold higher in patients with SLE) [25]. The most common causes include accelerated atherosclerosis, embolization, thrombosis, or vasculitis. Atherosclerosis is the most common coronary artery involvement in patients with SLE [26]. Coronary vasculitis is a rare condition; there are only a few case reports. It often occurs in the absence of clinical SLE flare and with minimal serologic evidence of disease activity [27]. The clinical differentiation of the atherosclerotic coronary artery disease coronary arteritis is difficult. Angiography is required for diagnosis; findings include isolated segments with tapered narrowing, the presence of coronary ectasia, or aneurysms. Histopathologically, there can be coronary artery thrombosis or deposition of immune complexes, with infiltration of lymphocytes and neutrophils and fibrinoid necrosis [28]. Recently, a case report has been published about a patient with inflammatory aortitis and progression of the aortic root and ascending aorta [29••].

Pulmonary Vasculitis

In the lungs, diffuse alveolar hemorrhage (DAH) usually occurs in fewer than 5 % of patients with SLE, and it is often concurrent with lupus nephritis [30]; however, DAH has been reported as the first manifestation of SLE in up to 20 % of patients [31]. Two types of DAH may occur in SLE; the most common finding at the lung biopsy is “bland” alveolar hemorrhage with inflammatory features but no vasculitis. Vasculitis of the small vessels with capillaritis, which is considered to be less frequent, has nevertheless been reported in up to 80 % at biopsy or postmortem examination [32•]. This presents clinically as progressive and severe dyspnea, fever, and hemoptysis in over 60 % of cases [33]. A chest radiography, CT, bronchoscopy, and bronchial lavage (if the patient's condition allows it) can be useful in the diagnosis. At histopathology, the presence of capillaritis and mononuclear infiltrates, alveolar necrosis, and immune complex deposits of IgG and C3 can be detected in up to 50 % of patients [34]. These changes are similar to lupus microangiopathy of the kidneys [35].

Retinal Vasculitis

At the ocular level, there are case reports of retinal vasculitis, which is a rare event that occurs as retinal hemorrhage and areas of vasoconstriction. The exact pathophysiology of the condition is unknown; however, deposits of

immune complexes, complement deposits, and antiphospholipid antibodies have been detected [36].

Nervous System Vasculitis

Nervous system involvement in SLE patients can be very heterogeneous, but it is definitively not uncommon; neuropsychiatric manifestations (NPs) occur in between 37 % and 90 % of patients with lupus. Of these, 13.5 % may have involvement of the peripheral nervous system, and the most common of these, peripheral sensory polyneuropathy, is the main condition in 36.7 %, followed by mixed neuropathy (sensory and motor) in 18.8 % of patients [37].

At the central level, cognitive dysfunction (55 %–80 %), headache (24 %–72 %), mood disorders (14 %–57 %), seizures (6 %–51 %), and cerebral vascular events (5 %–18 %) are more frequent [38].

Within the pathophysiology of NP involvement, noninflammatory vasculopathy, along with the presence of autoantibodies such as anticardiolipin, anti-P-ribosomal, or anti NMDA, are often the main actors in the etiology of central nervous system compromise. Inflammatory vasculopathy is rare and usually involves microvasculature [39].

The most common peripheral nerve syndrome seen in SLE is a mild to moderately severe symmetric sensorimotor polineuropathy. Nerve biopsy in this setting usually shows axonal degeneration or axonal depletation, frequently accompained by nonspecific vascular changes or chronic perivascular inflammation. Less often, a biopsy may show necrotizing vasculitis [40].

Vasculitis of cerebral vessels is rare, and its incidence in postmortem studies does not exceed 7 %–10 % of cases. Since serum or cerebro spinal fluid markers that specifically detect CNS vasculitis are not available and angiography may be negative if predominantly small vessels are involved, early biopsy is imperative to distinguish vasculitis from treatment complications such as infections or lymphoma. This distinction is crucial for an adequate early and aggressive treatment [41, 42]. Although it is a extremely rare association, there are four case reports of SLE patients with spontaneous spinal epidural haematoma and the pathological demostration of cervical spinal cord inflammatory vasculitis [43].

Kidney Vasculitis

The kidney is affected in one half to two thirds of patients with SLE, with a high incidence of proliferative nephritis, accompanied on a few occasions by vasculitis. The histological lesion of vasculitis is focal segmental necrotizing glomerulonephritis with fibrinoid necrosis, which may lead to rapid progressive renal failure [44]. Necrotizing inflammation of the larger arteriole and small artery involvement may also be found associated with several renal diseases [45].

Vasculitis Treatment

The primary basis of treatment is the suspected diagnosis and timely intervention. Cutaneous vasculitis treated with antimalarials usually shows an appropriate response; if there are any contraindications for the drug or a lack of efficacy, thalidomide and dapsone have shown good results [46]. Vasculitis with involvement of visceral organs is usually handled with corticosteroids and immunosuppressants for the long term, such as cyclophosphamide [47], azathioprine, or mycophenolate mofetil [48•]. It has been demonstrated by Barile et al. that aggressive treatment for serious nervous system manifestations such as multiplex mononeuropathy, seizures, and transverse myelitis is better, as demonstrated by the management based on methylprednisolone 3 g followed by cyclophosphamide for 2 years in their first group, with only 1 patient out of 19 presenting failure to treatment, as compared with the control group receiving only methylprednisolone [49, 50]. In pulmonary vasculitis, the massive treatment with methylprednisolone (>4 g) was better than conventional methylprednisolone (3-g total doses) or than oral prednisolone [51]. Other treatments that have shown good results are the administration of intravenous immunoglobulin [52] and biological therapy such as rituximab [53•]. There are new biological drugs such as belimumab [54••], which is a monoclonal antibody that inhibits activating factor B cells (BAFF), also called an activator of B-lymphocytes (BlyS), that may be used in patients refractory to the previously cited arsenal.

Conclusion

There is a heterogeneous presentation of vasculitis in the setting of SLE, SVV being the most frequent type, presenting as cutaneous lesions. Although MVV is infrequently associated with SLE, it represents an increased risk for morbidity and mortality. Differentiating among active SLE (hypocomplementemia; high anti-DNA; lymphopenia; active articular, cutaneous, or renal disease) associated APS (thrombosis, antiphospholipid antibodies, valvulopathy, thrombocytopenia), and associated systemic vasculitis is crucial. Early diagnosis and adequate treatment are recommended.

Compliance with Ethics Guidelines

Conflict of Interest Leonor Adriana Barile-Fabris, María Fernanda Hernández-Cabrera and Jorge Alberto Barragán- Garfias declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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Key Points

- Vasculitis in SLE may involve vessels of any size, but small vessel involvement predominates.
- Visceral vasculitis is associated with increased mortality.
- There is a close association between the presence of vasculitis and lupus activity.
- The presence of vasculitis in critical organs or systems (pancreas, kidney, central nervous system) requires aggressive treatment with high-dose steroids and immunosuppressive agents (cyclophosphamide).