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VASCULITIS (L ESPINOZA, SECTION EDITOR)

Lupus Vasculitis

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Abstract

Purpose of Review The purpose of this manuscript is to review the most recent literature pertinent to the presence of vasculitis in patients with systemic lupus erythematosus (SLE), including previously published landmark articles and studies and to update the different clinical and diagnostic aspects of vasculitic manifestations in patients with this important autoimmune disorder. As a multisystem autoimmune disease, systemic lupus may attack practically any organ system in the human body. Even though vasculitis is not the most common presentation or pathogenic mechanism of disease, it frequently causes significant morbidity and mortality in patients with SLE. The most common manifestation of lupus vasculitis is cutaneous involvement; visceral involvement is less common but causes severe disease; it may occur in different areas including central nervous system, peripheral nervous system, gastrointestinal system, kidneys, lungs and even retina.

Recent Findings Recent findings regarding the pathogenesis of lupus CNS and peripheral nerve disease, and vascular injury in lupus nephritis are reviewed as well.

Summary Vasculitis is an uncommon but serious manifestation of SLE; it may involve different organ systems and present in a wide variety of clinical syndromes, and thus the importance of its recognition and early diagnosis by physicians who deal with this disease, in order to start prompt and aggressive therapy when indicated.

Keywords Systemic lupus erythematosus · Vasculitis · Lupus enteritis · Lupus vasculitis

Introduction

Systemic lupus erythematosus (SLE) is the quintessential systemic autoimmune disorder, where autoimmune mechanisms such as auto antibody production lead to the potential attack of any organ system. It affects both genders and all races, being more common in females and minority group such as African Americans, Native Americans, and Hispanics [1].

Involvement of the blood vessels by systemic lupus has been recognized, and even though it is not the most common manifestation, it could lead to serious morbidity and mortality. Prevalence fluctuates between 11 and 35.9% [2], even though large studies and cohorts addressing specifically vasculitis in lupus are very few. It predominantly involves small vessels; medium-sized vessels can also be affected, and large vessel involvement is very rare [3].

Lupus patients with vasculitis tend to have longer disease duration and SLE starting at younger ages than those without vasculitis [4].

Ninety percent of the cases present as cutaneous vasculitis but visceral involvement can also occur, mainly in the form of mononeuritis multiplex. Lupus vasculitis tends to present more frequently during active disease and be accompanied with general inflammatory symptoms and laboratory abnormalities, such as fevers, malaise, weight loss, and elevated inflammatory markers, along with more specific manifestations depending on the area of involvement such as purpura and livedo reticularis [3].

In most cases, other manifestations of lupus precede the onset of vasculitis; it is the initial presentation in approximately 20% of the cases [3].

Since the majority of the cases are cutaneous, for the purpose of this review, we will divide lupus vasculitis into 2 categories, cutaneous lupus vasculitis and visceral lupus vasculitis.

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

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Cutaneous Lupus Vasculitis

The skin is one of the most common affected organs in SLE and skin vasculitis has been found in 8% of patients with cutaneous lupus lesions [5]. Cutaneous vasculitis may be seen in 19–28% of patients with SLE [6] and accounts for 89% of the cases of vasculitis in this disease [3]. Anti-Ro antibodies, positivity for cryoglobulins [7, 8], and antiphospholipid antibodies [4] have been associated with a higher prevalence of cutaneous vasculitis in lupus. Lupus vasculitis can be limited to skin or associated with nerve and visceral involvement [9•].

Histopathology demonstrates small-vessel involvement in most cases, but medium vessel vasculitis can also occur [10]. Clinical presentation is heterogeneous: the most common forms are erythematous punctate lesions on the fingertips and palms (36%) and palpable purpura (25%). Ulcers, urticarial, and nodular lesions have also been described, and up to 29% of patients have different types of lesions at the same time [3].

Morphologically, small-vessel vasculitic lesions in lupus may be identical to small-vessel vasculitis in other autoimmune conditions and may present with palpable purpuric areas as well as findings of leukocytoclastic vasculitis on pathology [10]. An analysis of 704 European lupus patients revealed a large variety of possible morphologic vasculitic cutaneous presentations including palpable purpura, petechiae, papulonodular lesions, livedo reticularis, cutaneous infarction, erythematous plaques, erythema with necrosis, panniculitis, splinter hemorrhages, and superficial ulcerations [3, 11].

Visceral Involvement

Internal organ involvement occurs in about 6–18% of cases of lupus vasculitis according to different series (SHARMA). Even though it is not frequent, visceral involvement is associated with increased mortality. The most common type of visceral involvement is mononeuritis multiplex, followed by digital necrosis and abdominal vasculitis [3, 4, 12].

CNS Involvement

Neuropsychiatric lupus is a serious complication of SLE, which may occur in 30% of the patients; however, active small-vessel vasculitis is less common. The main histopathologic finding of neuropsychiatric lupus erythematosus is a non-inflammatory microangiopathy in association with brain microinfarctions and thrombosis rather than active inflammatory changes of the vessels [2, 13].

Vasculitis is rarely confirmed as a cause of CNS vascular injury in SLE; other neurological manifestations are more common in this disease including stroke (both ischemic and hemorrhagic), SLE cerebral vasculopathy, and posterior reversible encephalopathy syndrome [14]. CNS vasculitis is thought to occur in approximately 1% of patients with SLE [15]. Clinical presentations include cognitive dysfunction, demyelinating syndrome, cerebrovascular disease, and seizures [15]. Although brain biopsy is the gold standard for the diagnosis its sensitivity is limited due to the segmental involvement of the vessels and there is a high surgical risk. Neuroimaging helps with diagnosis in most cases [15].

Cerebral angiography findings consist of segmental stenosis and dilation in multiple vascular territories; this technique however has important limitations in lupus-associated CNS vasculitis [16]. Small-vessel disease is beyond angiography resolution, thus usually not detected with this technique, [16] while large vessel involvement in lupus-associated CNS vasculitis is very rare [17]. Atherosclerotic disease can mimic central nervous system vasculitis on angiography [16]. Cerebrospinal fluid analysis is an important part of the workup mainly to rule out underlying infections due to bacterial, viral, fungal, and parasitic pathogens, since they can mimic CNS vasculitis [18]. Other abnormalities may be seen on the CSF of patients with neuropsychiatric lupus and vasculitis such as increased white blood cells and protein, decreased glucose, or an elevated IgG index, but they are very non-specific and usually not diagnostic since they can be seen in other inflammatory conditions such as multiple sclerosis [19].

Angiographic imaging is limited to the vessel lumen providing only indirect evidence of vessel wall thickening. MRI is now regarded as the most sensitive non-invasive image study for cerebral vasculitis [15]. MRI may demonstrate wall thickening and intramural contrast material uptake in vasculitis affecting large brain arteries. Contrast-enhanced MR angiography can help detect changes in the blood vessels such as luminal narrowing. Contrast-enhanced high-resolution MR imaging at 3.0 T may depict thickening and enhancement in the wall of large arteries [20]; however, MRI currently lacks the spatial resolution required to directly detect small-vessel involvement [21••].

Patterns and intensity of post gadolinium enhancement of vascular lesions using T1 post contrast vessel wall magnetic resonance imaging (VWI) have been used to differentiate between vasculopathies and intracranial atherosclerotic disease (ICAD). ICAD generally reveals eccentric thickening with variable enhancement, whereas vasculitis shows smooth, intense, and homogeneous enhancement, and reversible cerebral vasoconstriction syndrome (RCVS) has minimal to no enhancement and minimal wall thickening [22–24].

Gastrointestinal Involvement

Gastrointestinal vasculitis is an uncommon manifestation, but it is serious in many cases since it often presents with

ischemia and potential necrosis of the small or large bowel, which may lead to perforation and hemorrhage, and it is often accompanied by signs of active disease at other sites [12]. The superior mesenteric artery is most often involved in 80–85% of the cases affecting the ileum and the jejunum; involvement of the large bowel and the rectum is less frequent [12]. Vasculitis of the hepatic arteries has been reported as well [2].

Lupus enteritis occurs in 0.2–14.2% of SLE patients [25•, 26]. It can be the initial presentation of SLE in 48.5% of cases [27], but may also occur months to years after the diagnosis of SLE, with a mean of 4.85 years [28]. The most common presenting symptom is abdominal pain (90.7%) [27, 29]; in fact, it is the cause of 56.3% of admissions for acute abdominal pain in lupus patients [28].

It can also be associated to urinary symptoms like dysuria and frequency due to the coexistence of lupus enteritis with cystitis in 22.7% of cases [27]. Lupus enteritis is usually associated with active SLE, which coincides with higher scores in disease activity measures such as SLEDAI and BILAG and higher steroid doses in the 3 previous months in patients already diagnosed with SLE [29•]. Yuan et al. found that 62.9% of patients with lupus enteritis presented with other concomitant organ involvement, mainly kidneys (67%), heart (33%), joints (30.9%), serositis (22.7%), lungs (15.5%), and central nervous system (10.3%) [27]. Pathology specimens taken during endoscopic procedures are characterized by mucosal edema (100%) but could only show chronic inflammation; when biopsies are obtained by surgical intervention due to intestinal infarction, there is usually infiltration of inflammatory cells in vascular walls [27].

Histopathology, however, is not necessary to establish the diagnosis, which could be guided by tomographic findings of bowel wall thickening (3-mm thick in an area that was distended maximally and 5 mm for gastric wall), target signs, dilatation of intestinal segments (2.5 cm for the small bowel and 8.0 cm for the large bowel), engorgement of mesenteric vessels, and increased attenuation of mesenteric fat [27, 30], being the jejunum and ileum the most commonly involved locations [29•].

Evidence of multiple vascular territories and multifocal bowel involvement with skip lesions may indicate the presence of lupus enteritis [27]. Bladder wall thickening, hydroureteronephrosis, and stenosis or dilatation of the ureters can be present due to concomitant involvement of urinary tract [27]. Timely diagnosis of lupus enteritis is important to avoid life-threatening complications such as intestinal hemorrhage, infarction, and perforation. Despite successful treatment, lupus enteritis can relapse in up to 31.7% of cases, with a mean interval between the first and second attack of 24.4 months [28]. Risk factors for recurrence include colon involvement and presence of cystitis [30].

Digital Necrosis

Digital necrosis is generally rare in SLE, being identified in 0.67% of lupus patients [31], although some authors have found it to be more common [4]. It is characterized by discoloration and intense numbness or pain of the fingers or toes and usually occurs months or years after lupus onset, and most cases tend to present in patients receiving low doses of prednisone and no other immunosuppressants. Risk factors for the development of gangrene include disease duration and the presence of Raynaud's phenomenon [31].

Digital necrosis in SLE can be due to vasculitis but also to thromboembolism and atherosclerosis [32]. Peripheral vascular damage, in the form of atherosclerosis or thrombotic events, is much more common than vasculitis, with a prevalence of 5.3% in the LUMINA cohort, and it can present with minor or significant tissue loss in limbs, with gangrene and digit or foot loss [33]. Some patients with digital gangrene may not have evidence of active lupus; in those cases, it would be recommended to check for antiphospholipid antibodies [34].

Peripheral Nervous System Involvement

Peripheral neuropathy has been reported in 3.43% patients with SLE [35] and is the most common form of peripheral nervous system compromise related to lupus [36•].

Pathogenesis of SLE-related neuropathy is not completely understood, but pathological studies of peripheral nerves have reported inflammatory changes and vasculitis in some cases [37]. Peripheral nervous system SLE can be the only manifestation of a lupus flare (in 45.2% cases) or occur in the context of other SLE-associated clinical manifestations, mainly cutaneous and articular, and it is usually associated to a high disease activity by SLEDAI [36•]. Electrophysiological testing in patients with peripheral neuropathy or mononeuropathy usually reveal axonal damage but can also show demyelination, and most cases show a sensorimotor neuropathy, followed by isolated sensory neuropathy and less commonly isolated motor neuropathy [38].

Histology usually shows axonal degeneration or depletion, along with non-specific vascular changes or chronic perivascular inflammation. Less often, a biopsy may show necrotizing vasculitis [39]; some studies have shown a higher frequency of mononeuritis multiplex [3, 4].

Non-SLE-related peripheral neuropathies as nerve/root compression, medication toxicity, hypothyroidism, diabetes mellitus, ethanol abuse, paraproteinemia, uremia, and viral hepatitis must be considered during the diagnostic approach, given that they can explain 39.6% of cases [40].

Renal Vasculitis

Vascular injury is defined as arteriolar or arterial thickening of the intima with or without necrosis or proliferation [41•] which has been found in 67–81.8% of patients with lupus nephritis [41, 42]. Lupus renal vasculitis is an uncommon subtype of vascular renal injury, identified in just 0.6% of renal biopsies [42] and is characterized by prominent inflammatory cell infiltrate with mural inflammation and fibrinoid necrosis [43]. A multicenter Italian study reviewed renal biopsy samples of 285 patients with lupus nephritis and found that renal vascular lesions were common, present in 27% of specimens, but true vasculitis was uncommon (2.8%) [44]. The most common vascular abnormality found was the so-called lupus vasculopathy, a deposition of eosinophilic, PAS-positive material between the endothelium and the media. The second more common vascular lesion in this study was a HUS/TTP malignant hypertension-like injury characterized by intimal proliferation, lumen narrowing, edema, and thrombosis [44]. The prognostic value of vasculitis with regard to the risk of progression to ESRD and death in lupus nephritis has been postulated, but Leatherwood et al. found that the presence of vascular injury is a strong predictor of prognosis but not independent of serum creatinine and nephritis class [41•].

It is well-known that the most common renal pathology in lupus is glomerulonephritis; renal artery vasculitis may be seen as well in severe cases, although it is uncommon [12, 45].

It is believed that focal segmental necrotizing glomerulonephritis with fibrinoid necrosis is the typical histologic lesion of renal lupus vasculitis [2]. Immune complex deposition has been found to be frequent in patients with lupus nephropathy although the identification of true blood vessel inflammation is uncommon [42].

Pulmonary Vasculitis

Pulmonary vasculitis is uncommon [46], but it could be a severe manifestation of the disease; it is often associated with glomerulonephritis and renal involvement. The most common clinical presentation of systemic lupus in the lungs is diffuse alveolar hemorrhage (DAH).

DAH develops due to pulmonary endothelial or epithelial cell injury with disruption of the alveolar–capillary interface integrity, leading to entry of red blood cells into the alveolar spaces [47]. DAH occurs in 1–5.4% SLE patients and explains 1.5–3.7% of hospital admissions due to SLE. DAH usually presents early in the course of disease, being the initial lupus manifestation in 10–20% cases, and occurs in the context of high disease activity by SLEDAI, with multiple extra pulmonary manifestations, mostly hematological, constitutional, and renal as mentioned previously [48].

DAH must be suspected in the presence of new bilateral infiltrates on chest X-ray or computed tomography, unexplained drop of at least 1.5 g/dl in hemoglobin and at least one of the following situations: hypoxemia, hemoptysis, bloody broncho alveolar lavage or the presence of hemosiderin-laden macrophages on it, or hemosiderin-laden macrophages or capillaritis in a lung biopsy. Although frequent, hemoptysis is not essential for DAH diagnosis; it can be absent in 23.5% cases [49], and its frequency does not differ between SLE-DAH and other causes of acute diffuse lung infiltration in SLE patients [50•]. Capillaritis seen in DAH is similar to that seen in ANCA-associated vasculitis, although some studies have shown evidence of concomitant vasculitis of arterioles and small muscular arteries [51].

It should be emphasized that other conditions as heart dysfunction, pulmonary overload, and infections may also result in accumulation of red blood cells in alveoli and DAH [52]. Infections must always be ruled out, given that it has been demonstrated in 57% of SLE patients with DAH [53]. DAH is a deadly complication of SLE, with mortality rates of 35.3% [49], mainly associated with the need of mechanical ventilation [50], and may recur in 23.5% of cases [49].

Retinal Vasculitis

Retinal involvement has been described in 7–29%, but is mainly a vasculopathy due to complement activation and immune complex deposition [54] with microangiopathy or severe vaso-occlusion [55]. Retinal vasculitis is a subset of retinal vasculopathy characterized by inflammation of retinal venules or arterioles [54, 55]; it is a very uncommon complication with few case reports published in the literature and has been associated with the presence of antiphospholipid antibodies and immune complex deposition [54, 56]. Retinal vasculitis can be asymptomatic, especially when changes are located in the peripheral retina, or may present with blurred/decreased vision, visual field deficits, or even permanent visual loss. Given that histopathologic evidence is hardly available in the eye, diagnosis is based on indirect clinical signs. Retinal vessel sheathing is the main diagnostic sign on funduscopic examination, cotton wool spots, retinal hemorrhage, and vascular occlusion may also be seen [56]. Additional ophthalmic investigations such as fluorescein angiography and optical coherence tomography can be helpful to identify active retinal disease and to define the extent of retinal involvement [56, 57]. Infections must always be considered in the differential diagnosis given that pathogens like human immunodeficiency virus, syphilis, tuberculosis, toxoplasmosis, cytomegalovirus, and herpes simplex can produce retinal vasculitis more commonly than SLE by itself [58].

Treatment

There is a general lack of therapeutic randomized trials to help guide therapeutic decisions in lupus vasculitis; information is mainly based on case reports and small case series, and it is sometimes extrapolated from the management of other lupus manifestations and other vasculitides. In severe organ involvement, intravenous methylprednisolone pulse therapy or high-dose prednisone have been reported to be useful [26], and has been administered along with other immunosupressants, mainly cyclophosphamide or rituximab as induction therapy, and varying regimens of azathioprine, mycophenolate mofetil, and hydroxychloroquine for maintenance [14, 27, 29]. In skin-limited vasculitis, responses to colchicine [59], hydroxychloroquine [60], mycophenolate mofetil [61], and rituximab [62] have been reported in the medical literature.

Conclusion

Vasculitis is an important source for morbidity and mortality in patients with systemic lupus even though it is not the most frequent manifestation. Cutaneous vasculitis is the most common type of vasculitis in lupus, and it has many forms and clinical presentations. Visceral involvement is a lot less common; however, it could be severe and involve vital organs such as the central nervous system, lungs, kidneys, and GI tract. Visceral vasculitis usually requires heavy immunosuppression with corticosteroids and other agents such as cyclophosphamide.

Randomized controlled trials specific for lupus vasculitis have not been published, and the therapeutic decisions are typically made from experience treating other severe manifestations of lupus or other types of vasculitic syndromes.

In summary, it is very important for clinicians who treat systemic lupus patients to recognize vasculitis as an important and serious manifestation of the disease so they can be diagnosed and treated promptly in order to prevent serious morbidity and mortality.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts 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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