

What is lupus vasculitis? A case with diffuse alveolar hemorrhage

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Definition and Classification: Systemic lupus erythematosus (SLE) is a multifactorial systemic autoimmune disease caused by a loss of tolerance to self-antigens, mainly nuclear antigens (deoxyribonucleic acid, ribonucleic acid, and nuclear proteins). It is characterized by aberrant T- and B-cell responses, autoantibody production, and immune complex deposition in tissues with complement activation, inflammation, and irreversible organ damage [1]. SLE can affect any organ system as well as vessels, resulting in a wide range of clinical presentations. Lupus vasculitis prevalence fluctuates between 11 and 35.9%, even though large studies and cohorts addressing specifically vasculitis in lupus are very few [2]. It predominantly involves small vessels; medium-sized vessels can also be affected, and large vessel involvement is very rare [3,4]. It is difficult and controversial to completely separate the organ involvement of lupus from the vasculitis of lupus. For example, diffuse proliferative lupus nephritis and central nervous system involvement due to lupus are considered as vasculitic involvements by some authors. 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. Longer disease duration and younger age at the onset of the disease have been reported as risk factors for the development of LV [5,6]. In most cases, other manifestations of lupus precede the onset of vasculitis; it is the initial presentation in approximately 20% of the cases [7]. Vasculitides secondary to SLE are classified under the ‘vasculitis associated with systemic disease’

category according to the revised International Chapel Hill Consensus Conference (CHCC) nomenclature [8].

Clinical Features and Diagnosis: In ninety percent of SLE cases, vasculitis affects the skin. Internal organ involvement occurs in about 6–18% of cases of LV, according to different series. Even though it is not frequent, visceral involvement is associated with increased mortality [9]. The kidneys, gastrointestinal tract, nervous system (central and peripheral), retina, lungs, heart, and aorta can be involved with lower frequency [4,10-12].

Cutaneous Vasculitis: Cutaneous vasculitis is the most frequent type of vasculitis among patients with SLE. It is reported in up to 19–28% of patients with SLE [13,14]. High levels of anti-Ro and antiphospholipid antibodies (aPL) and positivity for cryoglobulins are associated with a major risk of developing cutaneous LV [5,15,16]. The clinical presentation of cutaneous LV is heterogeneous and includes palpable purpura, petechiae, papulonodular lesions, urticaria like, or bullous lesions of the extremities, livedo reticularis, cutaneous infarction, erythematous plaques or macules, erythema with necrosis, panniculitis, splinter hemorrhages, and superficial ulcerations [17]. Small vessels, principally post-capillary venules, are involved in most cases. Medium-vessel vasculitis is less frequent and appears as subcutaneous nodules or ischemic ulcers [4]. Myositis and hematological manifestations such as anemia, Coombs’ positivity, leucopenia, anti-Smith, and anti-RNP (ribonucleoprotein) may predict cutaneous vasculitis developments [18]. In

two large cohort studies in patients with vasculitis and SLE, the most frequent type of vasculitis was reported as leukocytoclastic vasculitis (60%), followed by cryoglobulinemic vasculitis (25–30%) and urticarial vasculitis (7%) [5,6].

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 [19]. It can also be seen as peripheral or central nervous system vasculitis (CNS). It is mostly seen in SLE patients with high disease activity. It is frequently seen in the form of non-inflammatory microangiopathy characterized by microinfarction and thrombosis in the brain, and rarely as inflammatory CNS vasculitis [20,21]. At the peripheral level, the most common clinical manifestation is the mononeuritis multiplex; histologically characterized by chronic axonal degeneration, necrotizing, or occlusive vasculitis of the vasa nervorum and demyelination. At the central level; cognitive dysfunction, demyelinating syndrome, cerebrovascular disease, and seizure are the most common clinical manifestations [22,23]. The diagnosis of central nervous vasculitis is a challenge for clinicians. A brain biopsy is the gold standard for the diagnosis, although it is a highly invasive procedure with a limited sensitivity due to the segmental nature of the vascular lesions. The combination of imaging (most often contrast-enhanced cranial magnetic resonance imaging (MRI), angiographic imaging) and other diagnostic tools help us in making an early diagnosis without biopsy [24].

Gastrointestinal Vasculitis: Gastrointestinal involvement is rare but severe as it often causes ischemia and potentially intestinal necrosis, perforation and bleeding. Lupus enteritis-lupus mesenteric vasculitis was reported in 0.2-14.2% of patients [25]. As a result of superior mesenteric artery (SMA) involvement with a rate of 80-85%, the ileum and jejunum are frequently affected. The colon, especially the rectum, is rarely affected. The gastrointestinal vasculitis most often presents with abdominal pain. The main diagnostic test is abdominal computed tomographic (CT) angiography; intestinal wall edema, target sign, and intestinal dilatation are expected images. Relapse has been reported in up to 32% of patients

[26]. Liver and pancreatic vasculitis have also been reported in 18-20% of autopsy cases [27].

Renal Vasculitis: Lupus nephritis (LN) is one of SLE's most common and severe manifestations. The renal histopathological lesions are closely associated with different clinical characteristics, therapeutic responses, and outcomes in LN patients [28], and can present as glomerular, tubulo-interstitial, and micro-vascular lesions. Renal microvascular lesions are common in LN and are becoming increasingly recognized as a hallmark of the disease. In addition to glomerulonephritis, there is accumulating evidence showing that renal vascular lesions can adversely affect long-term renal outcomes and might play an important role in the therapeutic strategy choice [29,30]. A diffuse proliferative glomerulonephritis is considered by some authors as the most frequent form of renal vasculitis involving glomerular capillaries. However, the general agreement is that these lesions should be classified as proliferative lupus glomerulonephritis [31]. Basically, 5 renal microvascular lesion types have been identified; these are (a) uncomplicated vascular immune complex deposits (ICD), (b) arteriosclerosis (AS), (c) non-inflammatory necrotizing vasculopathy (NNV), (d) thrombotic microangiopathy (TMA) and (e) true renal vasculitis (TV) [31].

Retinal Vasculitis: Retinal vasculitis is very rare and has only been published as case reports. Although the exact pathogenesis is unclear, it is thought that immune complex deposition, complement activation, and aPL play a role [32]. Typically, the precapillary superficial arterial vasculature is involved [33]. Retinal vasculitis can present as asymptomatic or with painless blurred vision, decreased vision, or permanent visual loss. A fundoscopic examination reveals retinal vessel sheathing, cotton wool spots, retinal hemorrhage, and vascular occlusion [34]. Retinal imaging, including fluorescein angiography and optical coherence tomography, can be helpful in the identification and characterization of retinal vasculitis [34,35].

Coronary Vasculitis: Coronary vasculitis is very rare and unlike other types of vasculitis, it was found to be weakly correlated with disease activity [36]. The diagnosis is usually made by serial coronary angiographies that disclose arterial aneurysms, tapered stenoses, and/or rapidly developing arterial occlusions [37].

Pulmonary Vasculitis: The most common clinical manifestation of lupus pulmonary vasculitis is diffuse alveolar hemorrhage (DAH) due to the erythrocyte extravasation into the alveolar spaces as a result of the widespread damage of the pulmonary vessels with disruption of the alveolar-capillary basement membrane [38]. The combination of dyspnea, hemoptysis, decrease in hemoglobin levels, decreased diffusing capacity for carbon monoxide, and pulmonary interstitial or alveolar infiltrates should warn about the possibility of DAH. This is particularly be considered for patients with active SLE [39]. A chest radiography, CT, bronchoscopy, and bronchial lavage can be useful in the diagnosis. Histopathologically, capillaritis and mononuclear cell infiltrates, alveolar necrosis, and immune complex deposits of IgG and C3 can be found [40]. These changes are similar to lupus microangiopathy of the kidneys [36].

Lupus Vasculitis and Antiphospholipid Syndrome: Often LV and APS coexist (especially with retinal, renal vasculitis and alveolar hemorrhage). The concomitant presence of vasculitis and APS is associated with a poor outcome [41,42].

Lupus Aortitis: Until now only 5 cases of lupus aortitis were reported. It can be seen at any age, the ascending aorta is most frequently involved in the form of wall thickening. The most striking finding is abnormal CRP elevation. Therefore, it was suggested to investigate aortitis in SLE patients with abnormal CRP elevation and could not be explained by other reasons [43].

Management: Therapeutic randomized trials to help the clinicians in LV are lacking, therefore information is mainly based on case reports and small case series.. Treatment modalities vary depending upon the presentation and severity of organ involvement. LV can be fulminant and life-threatening, thus prompt treatment is essential [44]. Cutaneous vasculitis often responds to antimalarials (hydroxychloroquine), dapsone or thalidomide. Short courses of corticosteroids may be used if a rapid response is desired [45]. For visceral involvement, intravenous methylprednisolone pulse therapy or high-dose prednisone have been reported to be useful [46], and has been administered along with other immunosuppressants, mainly cyclophosphamide or rituximab as induction therapy, and varying

regimens of azathioprine, mycophenolate mofetil, and hydroxychloroquine used for maintenance [47-49].

CASE PRESENTATION

A 33-year-old female patient was being followed up in the nephrology inpatient service because of acute renal failure requiring dialysis. She was admitted to the hospital with newly developed edema, shortness of breath and fatigue. Laboratory tests were performed and revealed a creatinine value of 5.2 mg/dl, BUN of 144 mg/dl, pleural-pericardial fluid and pulmonary edema were reported in thorax computed tomography, on echocardiography showed an ejection fraction of 65% and pericardial fluid without compression. Two years ago the patient was diagnosed as SLE due to arthritis, hematological involvement, antinuclear antibody (ANA) and dsDNA positivity as well. She was put on hydroxychloroquine of 200 mg/day, azathioprine of 100, and methylprednisolone treatment. The patient was consulted to the rheumatology clinic with newly developed complaints. She has constitutional symptoms, dyspnea, arthralgia of small joints of the hands, morning stiffness lasting almost three hours, oral aphthae at hard palate, Raynaud's phenomenon, and dryness on both mouth and eyes. Her physical examination was revealed a body temperature of 37.2 Celcius degree, a respiratory rate of 22 per minute, a pulse rate of 10 per minute, blood pressure of 154/92 mm/Hg; oropharyngeal examination revealed a palatal ulcer and crackles extending to bilateral medium lung zones. The cardiovascular system was rhythmic, tachycardic and there was bilateral pretibial edema. She was tendering in some of the small joints of the hands and the wrist. Laboratory tests at the time of rheumatology consultation was summarized in Table 1. Histopathological examination of the renal biopsy specimen showed a WHO class III focal lupus nephritis with an activity index of 19/24. Following the diagnosis of lupus nephritis 15 mg/kg/month cyclophosphamide iv treatment was started along with 3 days of 500 mg pulse methylprednisolone. The steroid was maintained at a dose of 1 mg/kg/day prednisolone. In the 1st month of the treatment, the patient complained of dyspnea requiring oxygen support, and hemoptysis. A thorax CT was consistent with

Table 1. Blood tests (biochemistry, hemogram and autoantibody panel)

	At the first application	At the time of alveolar hemorrhage
BUN (7-18 mg/dl)	39	45
Creatinine (0.6-1.1 mg/dl)	4.42	3.49
Aspartate Aminotransferase (5-34 U/L)	16	18
Alanine Aminotransferase (0-55 U/L)	15	25
CRP (0-5 mg/dl)	1.96	7.01
ESR (<20 mm/h)	124	
WBC (4.000-10.000)	5.130	8.590
Neutrophil (2.000-7.000)	4.480	7.950
Lymphocyte (800-4000)	470	390
Hemoglobin (12-16 g/dl)	9.3	8.3
Platelet (150.000-400.000)	304.000	98.000
Complete urine analysis:	Protein 4+ 20 erythrocytes+	
ANA	Homogeneous positive in 1/1000 titre	
ENA	Anti ds DNA ++ Anti Sm +++ Nucleosome +++ Ro-52 + SS-A +++ Histone ++ nRNP/Sm +++	
ANCA	Negatif	
C3 levels (90-180 mg/dl)	52.9	
C4 levels (10-40 mg/dl)	8.49	
Anti cardiolipin antibodies IG M and G (<7/<10 U/L)	3.0/2.3	
Lupus anticoagulant (0.9-1.1 sn.)	0.96	

BUN: Blood urea nitrogen, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, WBC: White blood cell, ANA: Antinuclear antibody, ENA: Extractable nuclear antigens, PR3 ANCA: Proteinase 3 antineutrophil cytoplasmic antibodies MPO ANCA: Proteinase 3 antineutrophil cytoplasmic antibodies

alveolar hemorrhage (Figure 1). Since pneumonia could not be ruled out initially, meropenem and teicoplanin were started. In this application 1 g pulse methylprednisolone treatment was repeated for 3 days, plasma exchange was performed for 5 times as well as 2nd cycle of cyclophosphamide treatment was given and steroid treatment was increased to 2/kg/day prednisolone. In the follow-up, a posteroanterior chest radiographs taken and the findings consistent with alveolar hemorrhage had resolved (Figure 2). After six cycles of cyclophosphamide treatment, the patient was in remission, and she underwent a renal transplantation from a living donor. The patient is now under stable follow-up condition.

Key messages

Vasculitis is seen at a rate of 11-35.9% in SLE and causes serious morbidity and mortality. It usually affects the small, less frequently the medium-sized vessels. Although cutaneous vasculitis is the most common manifestation, it can affect all organs.

Internal organ involvement occurs in about 6–18% of cases of LV according to different series. Even though it is not frequent, visceral involvement is associated with increased mortality.

Treatment modalities vary depending upon the presentation and severity of organ involvement. LV can be fulminant and life-threatening, thus prompt treatment is sometimes became essential.

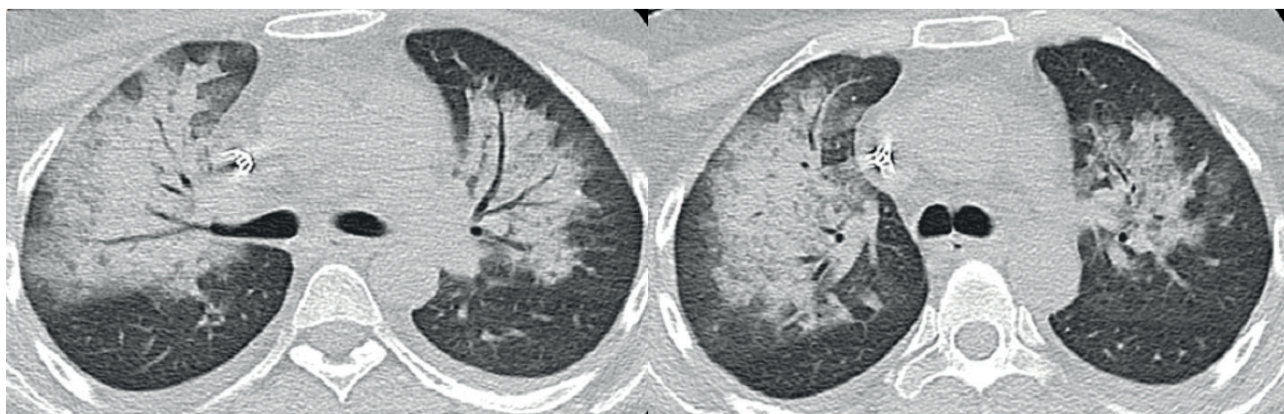


Figure 1. Computed tomographic images of bilateral alveolar infiltrates suggestive of diffuse alveolar hemorrhage.

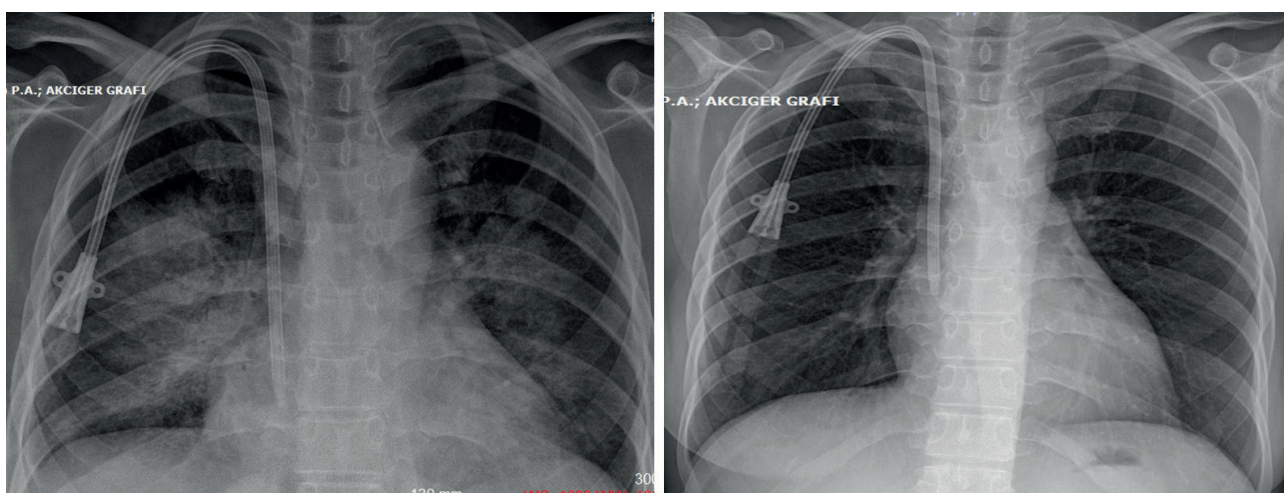


Figure 2. Posteroanterior chest radiographs taken during the active period of alveolar hemorrhage and two weeks later.

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