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ORIGINAL ARTICLE

Lupus-related vasculitis in a cohort of systemic lupus erythematosus patients

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ABSTRACT

Objectives: This study aims to examine the frequency and clinical association of lupus-related vasculitis in patients with systemic lupus erythematosus (SLE).

Patients and methods: We retrospectively analyzed medical records of a total of 565 SLE patients (42 males, 523 females; mean age: 32.7±9.5 years; range, 13 to 63 years) between January 2017 and February 2020. Demographic, clinical data, and laboratory data and treatment modalities applied were recorded. Lupus-related vasculitis and its different types were documented, and the patients with vasculitis were compared with those without vasculitis.

Results: The mean disease duration was 8.9±6.3 years. Vasculitis associated with lupus was found in 191 (33.45%) patients. Cutaneous vasculitis was found in 59.2%, visceral vasculitis in 34.0%, and both in 6.8% of total vasculitis patients. The patients with vasculitis had a longer disease duration (p=0.01), were more likely to have juvenile onset (p=0.002), livedo reticularis (p<0.001), Raynaud's phenomenon (RP) (p<0.001), digital gangrene (p<0.001), thrombosis (p=0.003), and cranial neuropathy (p=0.004). The patients with vasculitis showed a higher prevalence of hypercholesterolemia (p=0.045), diabetes mellitus (p=0.026), higher Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) at disease onset (p<0.001), and Systemic Lupus International Collaborating Clinics (SLICC) Damage Index (p=0.003) scores. They had more prevalent hematological manifestations (p<0.001), hypocomplementemia (p=0.007), received a higher cumulative dose of intravenous methylprednisolone (p<0.001), and had also more frequent cyclophosphamide (p=0.016) and azathioprine intake (p<0.001). In the logistic regression analysis, SLE vasculitis was independently associated with juvenile disease onset, livedo reticularis, RP, hematological manifestations, and higher scores of SLEDAI at disease onset (p<0.05).

Conclusion: Juvenile disease onset, livedo reticularis, RP, hematological manifestations, and higher SLEDAI scores at disease onset may be associated with the development of vasculitis in SLE patients.

Keywords: Clinical association, frequency, lupus vasculitis.

Systemic lupus erythematosus (SLE) is a multi-systemic autoimmune disease with different forms of clinical characteristics and serological features.[1] Although the pathogenesis of SLE has not been fully understood, loss of self-tolerance and activation of autoreactive T and B cells occurs, leading to the production of pathogenic autoantibodies and tissue injury that characterize the disease.[2] Vasculitis is inflammation of blood vessel wall,[3] characterized by infiltration of

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inflammatory cells and subsequent necrosis of vessel walls.[4] The term secondary vasculitis is used to describe inflammation of blood vessels occurring as a complication of underlying disease process (mainly systemic autoimmune diseases as SLE) or triggered by exogenous factors such as infection, drugs, or malignancy.[5] Lupus vasculitis is classified according to the updated Chapel Hill consensus criteria as vasculitis associated with systemic disease, among secondary vasculitides.[6] Systemic lupus erythematosus-associated vasculitis may present with different clinical courses,[7] depending on the site and size of the affected vessels,[8] the broad spectrum of symptoms and prognosis may range from mild forms, affecting only cutaneous vessels, to severe, catastrophic forms, with organs complications development, and vasculitis within the internal organs which may be life-threatening.[7,9] Vasculitis can be associated with disease flares in SLE,[10,11] and may manifest in as high as 56% of lupus patients throughout their life, with impact on prognosis. The earlier vasculitis is treated, the better is the prognosis of SLE.[12]

On the other hand, there are still limited data about the classification and characteristics of the vasculitides associated with systemic autoimmune diseases as SLE. In the present study, therefore, we aimed to investigate the frequency and clinical association of lupus vasculitis in a cohort of SLE patients.

Table 1. Demographic and clinical characteristics of SLE patients with and without vasculitis

	SLE patients (n=565)						
	With lupus vasculitis (n=191)			Without lupus vasculitis (n=374)			
Variables	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			32.1±9.3			32.9±9.6	0.3
Sex							0.69
Female	178	93.2		345	92.2		
Male	13	6.8		29	7.8		
Disease duration (year)			9.8±6.5			8.4±6.2	0.01*
Juvenile disease onset	61	31.9		76	20.3		0.002*
Constitutional manifestations	146	76.4		276	73.8		0.49
Mucocutaneous manifestations	176	92.1		329	88.0		0.13
NPSLE	87	45.5		153	40.9		0.29
Cranial neuropathy	9	4.7		3	0.8		0.004*
Peripheral nerve involvement	14	7.3		22	5.9		0.51
Nephritis	126	66.0		264	70.6		0.26
Renal failure	15	7.9		16	4.3		0.08
Arthritis	178	93.2		341	91.2		0.41
Cardiovascular manifestations	56	29.3		97	25.9		0.39
Pulmonary manifestations	113	59.2		210	56.1		0.49
Pulmonary hypertension	21	11.0		38	10.2		0.76
Serositis	108	56.5		200	53.5		0.49
GIT manifestations	22	11.5		32	8.6		0.26
Livedo reticularis	16	8.4		7	1.9		<0.001*
Raynaud's phenomenon	72	37.7		80	21.4		<0.001*
Digital gangrene	15	7.9		4	1.1		<0.001*
Thrombotic events	43	22.5		48	12.8		0.003*
Sicca manifestations	28	14.7		49	13.1		0.61

SLE: Systemic lupus erythematosus; SD: Standard deviation; NPSLE: Neuropsychiatric SLE; GIT: Gastrointestinal tract; * Significant differences (p<0.05).

PATIENTS AND METHODS

This retrospective multi-center study was conducted at Cairo and Beni Suef University Hospital, Department of Rheumatology between January 2017 and February 2020. A total of 565 SLE patients (42 males, 523 females; mean age: 32.7±9.5 years; range, 13 to 63 years) who fulfilled the Systemic Lupus International Collaborating Clinics (SLICC) classification criteria[13] were included. Medical records were reviewed for demographic data, clinical manifestations, routine laboratory investigations and immunological profile including antinuclear antibody (ANA), anti-double stranded deoxyribonucleic acid (anti-DNA), serum complement (C3), and antiphospholipid antibodies (aPL). Also, Systemic Lupus Erythematosus Disease Activity Index (SLEDAI)[14] was used at the first visit and the last visit for each patient. Accumulated damage was reported according to the SLICC/American College of Rheumatology-Damage Index (ACR-DI).[15] The details of medical treatment including the total dose of intravenous methylprednisolone and total dose of cyclophosphamide prescribed to the patients since SLE diagnosis, and across all exposure periods until the time of data collection were documented. The study protocol was approved by the National Research Centre Ethics Committee (NRC 20183). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Vasculitic lesions in our series were divided into cutaneous and visceral vasculitis. Similar to Kallas et al.,[16] clinical diagnosis of cutaneous vasculitis was done by an experienced rheumatologist and/or dermatologist (not essentially through histopathology), particularly in typical sites such as palms, soles, fingertips, when a patient presented with palpable purpura or erythematous punctuate lesions in palms, soles, or finger tips not related to palm erythema. Skin lesions related to conditions other than vasculitis such as neoplasms, drug reactions, and SLE-specific cutaneous lesions were excluded. In doubtful cases of cutaneous vasculitis, the definite diagnosis was confirmed by skin biopsy and histopathological reports showing typical findings of lupus-related cutaneous vasculitis.[17] Visceral vasculitis was confirmed by contrast-enhanced magnetic resonance imaging (MRI) for brain vasculitis, while fundal fluorescein angiography (FFA) was performed for retinal vasculitis, Duplex ultrasound for peripheral arteries, thoracic computed tomography (CT) for intra-alveolar hemorrhage, CT angiography for mesenteric vasculitis, electrocardiography (ECG) and coronary angiography for coronary vasculitis, and nerve biopsy for mono-neuritis multiplex.

Systemic lupus erythematosus-related vasculitis was classified according to the classification of Jennette and Falk[3] using the names and definitions adopted by the Chapel Hill Consensus Conference.[18]

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). Quantitative data were expressed in mean ± standard deviation (SD) for normally distributed data and in median and interquartile range (IQR) for non-normally distributed data. Qualitative data were expressed in number and frequency. The chi-square test was used for testing the association between categorical variables. The Fisher's exact test was used, when the expected frequency count

Table 2. Distribution of vasculitis in lupus patients according to the organs affected

Site of vasculitis	Secondary vasculitis lupus patients (n=191)	
	n	%
Vasculitis affecting single organ		
Skin vasculitis	113	59.2
Brain vasculitis	14	7.3
Retinal vasculitis	23	12
Peripheral limbs vasculitis (arteritis)	13	6.8
Intra-alveolar hemorrhage	6	3.1
Mesenteric vasculitis	2	1.0
Coronary vasculitis	1	0.5
Mononeuritis mutiplex	3	1.6
Vasculitis affecting more than one organ		
Skin and retinal vasculitis	8	4.2
Skin and brain vasculitis	1	0.5
Skin and limb arteries	1	0.5
Skin and lung	1	0.5
Skin and coronaries	1	0.5
Brain and retinal vasculitis	2	1.0
Brain and lung	1	0.5
Skin, brain and retinal vasculitis	1	0.5

Table 3. Relation between each of comorbidities, disease activity and damage indices, and vasculitis in lupus patients

	SLE patients (n=565)									
	With vasculitis (n=191)					Without vasculitis (n=374)				
Variables	n	%	Mean±SD	Median	IQR	n	%	Mean±SD	Median	IQR	*p*
Systemic hypertension	86	45.0				149	39.8				0.24
Diabetes mellitus	24	12.6				26	7.0				0.026*
Dyslipidemia (n=531)	89/182	48.9				161/349	46.1				0.54
Hypercholesterolemia (n=531)	76/182	41.8				115/349	33.0				0.045*
Hypertriglyceridemia (n=531)	71/182	39.0				109/349	31.2				0.072
Thyroid disease	17	8.9				25	6.7				0.34
AVN	21	11.0				28	7.5				0.16
SLEDAI at onset			16.1±10.4					11.8±7.3			<0.001*
SLEDAI at last visit				2	0-6				4	0-8	0.23
SLICC-DI				1	0-2				1	0-2	0.002*

SLE: Systemic lupus erythematosus; SD: Standard deviation; IQR: Interquartile range; AVN: Avascular necrosis; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SLICC-DI: Systemic Lupus International Collaborating Clinics-Damage Index; * Significant differences (p<0.05).

was <5. The Student t-test was done to analyze statistically significant differences between the two groups. The Mann-Whitney U test was performed to compare between non-parametric data of two independent groups. Logistic regression analysis was used to estimate the dependence of SLE secondary vasculitis on a set of independent variables. A *p* value of <0.05 was considered statistically significant.

RESULTS

The majority of patients were attending Cairo University hospitals during the period from January 2017 until February 2020, while 70 patients were attending Beni Suef University hospitals during the period from January 2019 until February 2020. The mean disease duration was 8.9±6.3 (range, 0.5 to 34) years. Demographic and clinical

Table 4. Laboratory investigations, immunological profile, and medications in lupus patients with and without vasculitis

	SLE patients (n=565)									
	With vasculitis (n=191)					Without vasculitis (n=374)				
Variables	n	%	Mean±SD	Median	IQR	n	%	Mean±SD	Median	IQR	*p*
Hematological manifestations	187	97.9				336	89.8				<0.001*
24 h protein in urine at first (gm/day)				1	0.02-2.7				1.03	0-2.24	0.83
Consumed C3 (n=529)	131/186	70.4				201/343	58.6				0.007*
Positive ANA (n=552)	184/188	97.9				360/364	98.9				0.34
Positive anti ds-DNA (n=490)	127/169	75.1				222/321	69.2				0.17
Positive aPL antibodies (n=414)	70/149	47.0				111/265	41.9				0.32
Medications received											
Intravenous methylprednisolone intake	177	92.7				283	75.7				<0.001*
Cumulative intravenous methyprednisolone dose (g)			5.1±3.6					3.6±2.4			<0.001*
Cyclophosphamide intake	116	60.7				187	50.0				0.016*
Cumulative cyclophosphamide dose (g)			5.8±3.6					6.1±3.3			0.37
AZA	163	85.3				270	72.2				<0.001*
MMF	57	29.8				89	23.8				0.12
Antimalarial drugs intake	181	94.8				354	94.7				0.96

SLE: Systemic lupus erythematosus; SD: Standard deviation; IQR: Interquartile range; C: Complement; ANA: antinuclear antibody; Anti ds-DNA: Anti-double-stranded deoxyribonucleic acid; aPL: Antiphospholipid antibodies; AZA: Azathioprine; MMF: Mycophenolate mofetil; * Significant differences (p<0.05).

Table 5. Independent factors for lupus vasculitis

Variables	B coefficient	OR	(95% CI) for B	*p*
Disease duration	0.001	1.001	0.966-1.036	0.977
Juvenile disease onset	0.524	1.688	1.032-2.761	0.037*
Livedo reticularis	1.449	4.259	1.186-15.289	0.026*
Raynaud's phenomenon	0.504	1.655	1.044-2.624	0.032*
Hematological manifestations	1.371	3.938	1.294 -11.982	0.016*
SLEDAI at disease onset	0.052	1.053	1.028-1.080	<0.001*
SLICC-DI	0.074	1.007	0.947-1.224	0.258
Hypocomplementemia	0.28	1.323	0.842-2.078	0.225
Hypercholesterolemia	-0.007	0.993	0.639-1.544	0.976
Diabetes mellitus	0.424	1.528	0.765-3.054	0.23
Constant	-3.18	0.042	-	-

OR: Odds ratio; CI 95%: Confidence interval 95%; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SLICC-DI: Systemic Lupus International Collaborating Clinics-Damage Index.

data of the patients with and without vasculitis are shown in Table 1.

Lupus-related vasculitis was found in 191 (33.45%) of our patients, cutaneous vasculitis in 113 (59.2%) SLE patients, visceral vasculitis in 65 (34.0%) lupus patients, and combined cutaneous and visceral in 13 (6.8%) patients. The body organs involved in patients with vasculitis are shown in Table 2.

Comparison between the patients with and without vasculitis in our cohort regarding comorbidities (SLEDAI-SLICC) showed that total cholesterol, the estimated SLEDAI at disease onset, and SLICC scores were statistically significantly higher in the group of vasculitis. However, there was no statistically significant difference between the two groups regarding the SLEDAI scores at the last visit (Table 3). Mortality rate was significantly higher in the vasculitis group: the mortality rate in patients with vasculitis was 12% (23/191) versus 3.7% (14/374) in patients without (p<0.001). Also, comparison of both groups regarding laboratory findings showed that the vasculitis group had a statistically significant difference regarding hematological

Table 6. Independent factors for visceral vasculitis

Variables	B coefficient	OR	(95% CI) for B	*p*
Age	-0.027	0.973	0.944-1.004	0.085
Sex	0.383	1.466	0.412-5.216	0.554
NPSLE	1.08	2.945	1.697-5.111	<0.001*
Renal failure	-0.923	0.397	0.087-1.805	0.232
Digital gangrene	2.348	10.462	3.275-33.420	<0.001*
Thrombosis	0.803	2.232	1.183-4.210	0.013*
Thrombocytopenia	0.606	1.832	1.056-3.179	0.031*
SLEDAI at disease onset	0.055	1.056	1.028-1.085	<0.001*
Constant	-3.083	0.046	-	-

OR: Odds ratio; CI 95%: Confidence interval 95%; NPSLE: neuropsychiatric systemic lupus erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index.

manifestations and C3 consumption, compared to the other group.

The medications used are shown in Table 4. Lupus patients with vasculitis tended to receive higher cumulative doses of intravenous methylprednisolone and to have a higher frequency of cyclophosphamide and azathioprine intake compared to the other group, indicating a statistically significant difference ($p=0.016$, $p<0.001$, respectively).

In the logistic regression analysis, vasculitis in SLE was significantly associated with juvenile onset of lupus disease, livedo reticularis, Raynaud's phenomenon, hematological manifestations, and higher scores of SLEDAI at the onset of the disease (Table 5). On analyzing associated clinical features and laboratory investigations by logistic regression, the visceral vasculitis was significantly associated with neuropsychiatric SLE (NPSLE), digital gangrene, thrombosis, and thrombocytopenia (Table 6).

DISCUSSION

Vascular involvement is common in SLE patients and is implicated as one of the most frequent causes of mortality in established disease.[19] Vasculitis in SLE is among the most typical processes involved in the clinical evolution of the disease.[20] The presence of vasculitis appears to be an important turning point in disease process in SLE,[7] as it can adversely affect the disease outcome and change therapeutic decisions.

In the current study, SLE-related vasculitis was found in 33.5%. Similarly, the frequency of vasculitis in SLE patients ranges from 11 to 36% in the literature.[4,5,21] It has been also reported that about 21 to 70% of SLE patients may develop systemic vasculitis at some point of their illness.[22] In the present study, the patients with vasculitis tended to have a longer disease duration and juvenile onset compared to those without vasculitis, consistent with previous results.[21,23] Females represented 93.2% among lupus vasculitis cases, which is compatible with the Shahin et al.'s[24] study reporting as 94.6% females among vasculitis cases secondary to SLE. Previous studies reported that cutaneous vasculitis was the most predominant type of vasculitis in SLE patients occurring up to six to eight times more frequently than visceral vasculitis.[5,21] Likewise, our study showed that cutaneous vasculitis was more common (1.7-fold) than visceral vasculitis. The higher percentage of visceral vasculitis in our study may be due to the inclusion of retinal vasculitis which was present in 12% of patients. Retinal involvement in SLE patients has been described in 7 to 26% of cases in the literature.[25]

In the present study, similar to previous studies, a significant association of vasculitis with clinical manifestations as livedo reticularis,[5,21] and Raynaud's phenomenon[21,26] was found. Digital gangrene and thrombotic events were significantly higher in our lupus vasculitis cohort. Supportively, Crowson and Magro[27] reported that digital infarctions suggested underlying vasculitis, unless they were a result of Raynaud's phenomenon. Emmi et al.[28] showed that, although inflammation-induced thrombosis was considered a feature of autoimmune diseases as SLE, it also played a role in systemic vasculitis. Cranial neuropathy was found to be significantly associated with vasculitis group in our study; however, the limited number of data in the literature and a few number of patients with cranial neuropathy in our study suggest that further studies are needed to confirm this finding.

It is worth noting that patients with lupus vasculitis in our cohort had a significantly higher total cholesterol levels and a higher frequency of diabetes mellitus (DM) compared to the other group. It is well known that patients with DM are significantly at an increased risk for vascular complications with changes in cellular homeostasis and regulation of vascular physiology which, in turn, have an impact on the major functions of vascular cells.[29,30] Additionally, dyslipidemia has a definite effect on cardiovascular disease and subclinical atherosclerosis. Synergistically, DM and dyslipidemia contribute to increased vascular morbidity in autoimmune diseases as SLE.[31]

A higher frequency of hypocomplementemia in the vasculitis group was elicited in the present study, coinciding with the previously reported studies.[5,7,22] The presence of hypocomplementemia has been explained

as a part of disease pathogenesis involving immune complex deposition in the vessel wall.[32] Although, as previously described, many clinical and laboratory parameters were significantly associated with vasculitis, logistic regression analysis showed that the main association of lupus vasculitis in our cohort was juvenile onset of lupus disease, livedo reticularis, Raynaud's phenomenon, hematological manifestations, and higher scores of SLEDAI at the onset of the disease. Drenkard et al.[21] reported an association of Raynaud's phenomenon with lupus vasculitis in SLE in the univariate and multivariate analyses. A higher incidence of hematological manifestations as anemia,[5] and leucopenia[21,22] in the group with vasculitis was elicited in the aforementioned studies, as well as in the present study. Visceral vasculitis in SLE patients was significantly associated with NPSLE, digital gangrene, thrombosis and thrombocytopenia, and higher scores of SLEDAI at the onset of disease. NPSLE may occur as a result of impaired vascular supply due to vasculitis of cerebral vessels and increased risk of thrombosis.

In the current study, the vasculitis group tended to receive a higher cumulative dose of intravenous methylprednisolone, as well as a higher intake of cyclophosphamide and azathioprine. Indeed, this could be expected, as lupus vasculitis tends to occur more commonly during the disease flares.[5,7,21] This is supported by the fact that vasculitis is a well-recognized item of several disease activity assessment tools, including the SLEDAI.[14]

Nonetheless, there are some limitations to this study. Biopsy was unavailable for all cutaneous vasculitis patients. Full aPL profile was unable to be documented in some medical records of our patients, also anti-Ro and anti-La antibodies were excluded from our analysis, as they were missing in more than 25% of our medical records. Therefore, we recommend that further studies should be conducted to investigate the role of these autoantibodies as predictors of lupus vasculitis.

In conclusion, juvenile onset lupus, longer disease duration, livedo reticularis, Raynaud's phenomenon, hematological manifestations, and higher SLEDAI scores at the onset of the disease are associated with lupus vasculitis. Nevertheless, further studies are warranted to confirm whether they have an association or represent risk factors for the development of lupus vasculitis.

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