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Prognostic Value of Livedo Reticularis and Raynaud's Phenomenon in Systemic Lupus Erythematosus Patients

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Abstract

Background: Systemic lupus erythematosus is a chronic multisystem autoimmune inflammatory disease. Skin is considered as the second most commonly affected organ in lupus patients. Livedo reticularis and Raynaud's phenomenon are considered as cutaneous vascular manifestations of nonspecific skin changes that occur in systemic lupus erythematosus.

Aim of Study: This study aims to examine the frequency of Raynaud's phenomenon and livedo reticularis in SLE patients and its relation to disease outcomes.

Patients and Methods: This study is a post hoc analysis of previous study titled (Disease characteristics in patients with juvenile- and adult-onset systemic lupus erythematosus) conducted in Kasr Al-Aini Medical Hospital from October 2023 to April 2024. In the current study we retrospectively analyzed medical records of a total of 422 SLE patients, according to presence or absence of livedo reticularis and Raynaud's phenomenonpatients were divided in groups, and comparative studies between groups were conducted regarding demographic, clinical, and laboratory parameters. Furthermore, groups were compared regarding SLE Disease Activity Index (SLEDAI), and the Systemic Lupus International Collaborating Clinics/American College Rheumatology Damage Index scores (SLICC).

Results: The mean of disease duration was 9.7±6.7. Livedo reticularis and Raynaud's were more frequent in juvenile onset lupus patients (p=0.043, p=0.002). Livedo reticularis and Raynaud's patients showed statistically significant higher frequency of thrombosis (p<0.001, p=0.004), secondary vasculitis (p=0.017, p<0.001), digital gangrene (p<0.001, p=0.003), more frequent APL Antibodies (p=0.013, p=0.005) and higher damage index (p<0.001, p=0.031). Livedo patients showed statistically significant higher frequency of neuropsychiatric manifestations (NP), musculoskeletal manifestations, Hypocomplementemia (p<0.001, p=0.036, p=0.039), and higher frequency of dyslipidemia and renal failure (p=0.011, p=0.040), while Raynaud's patients showed higher frequency of avascular necrosis (p=0.001).

On comparing Patients with livedo and/or Raynaud's to those without, patients with livedo and or raynaud's showed statistically significant higher SLICC damage index (p=0.018), secondary vasculitis (p<0.001), NP (p=0.036), thrombosis (p=0.002), and more frequent APL antibodies (p=0.003).

Conclusion: Lupus patients with Raynaud's and/or livedo reticularis may be associated worse disease outcomes and higher damage index.

Key Words: *Livedo reticularis – Raynaud's phenomena – SLICC damage index – SLE.*

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Introduction

SYSTEMIC lupus erythematosus (SLE) is a chronic multisystem autoimmune inflammatory disease **[1].** Skin is considered as the second most commonly affected organ in lupus patients with skin manifestations occurring in 70–85% of the cases, and may be a presenting symptom in 25% of cases **[2].** Livedo reticularis (LR) and Raynaud's phenomenon (RP) are considered as cutaneous vascular manifestations of nonspecific skin changes that occur in SLE **[2,3,4].** LR is a transient or persistent clinical cutaneous finding which may present as reddish-blue to purple net-like skin discoloration and is a consequence of cutaneous blood flow disturbance that may occur in a variety of benign and pathologic condition **[5].** The livid rings in all forms are caused by reduced blood flow and lowered oxygen tension at the peripheries of the skin segments **[6,7].** LR has been found more

frequently in patients with positive antiphospholipid antibodies [8], and have been considered by some authors as a significant preceding sign for development of neuropsychiatric lupus erythematosus [9,10].

RP is caused by vasospasm of the small vessels especially those of the fingers, toes and in some occasions it may also involve small vessels of the internal organs. RP is triggered by cold and/or emotional stress, this vasospasm results in pallor, cyanosis and reactive hyperemia [11]. The association of RP was reported in 18–46% of SLE patients [12, 13]. The association of RF and LR with specific lupus clinical manifestations or different disease course is not well studied yet, and is a subject of controversy [13,14]. Thus in the current study we aimed to evaluate the prognostic value of RP and LR in SLE patients.

Patients and Methods

This study is a post hoc analysis of a previous study titled (Disease characteristics in patients with juvenile- and adult-onset systemic lupus erythematosus) [15], which is a retrospective multicenter comparative study conducted on 422 SLE patients, of them 186 were classified as Juvenile SLE (JSLE) (age at onset ≤16 years) and 236 were classified as Adult SLE (ASLE) (age at onset >16 years). The original study was approved by the participating department and conducted in accordance with good clinical practice, The current study was approved by the authors of the original study and by the ethical committee of the National Research Center (NRC) under number 4416072022.

In the current study patients were divided according to presence or absence of LR into two groups and were compared regarding demographic, clinical and laboratory findings, also both groups were compared regarding mortality, SLE Disease Activity Index at onset and last visit (SLEDAI) [16] and Systemic Lupus International Collaborating Clinics (SLICC)/ACR Damage Index (SDI) [17]. Similar comparison was conducted in our cohort according to presence or absence of RP and finally patients with LR and or RP were compared to those without.

Statistical analysis:

Data was coded and entered to the SPSS version 25 for windows 10. Categorical variables were presented as number and percent while numeric variables were presented as mean and standard deviation for normally distributed variables and median and interquartile range for not normally distributed variables. Association between categorical variables was done using Chi-Squared test or Fisher Exact test when possible. Comparison between 2 categories regarding normally distributed scale variables was done by independent *t*-test and Mann-Whitney U test for not normally distributed variables. *p*-value was considered significant at less than 0.05.

Results

This study enrolled 422 SLE patients, 376 (89.1%) female and 46 (10.9%) male, 186 (44.1%) were JSLE and 236 (55.9%) were ASLE. The median of disease duration was 9 (years) with a mean 9.7±6.7 (years). Details of demographic data are shown in (Table 1).

Table (1): Demographic characteristics for patients included in the study.

Items	Values (N=422)	
	No.	%
Sex:	376	89.1
Female	46	10.9
Male		
Age:		
Mean ± SD	30±9.3	
Median	30 (24, 37)	
Type:		
Juvenile	186	44.1
Adult	236	55.9
Disease duration:		
Mean ± SD	9.7±6.7	
Median	9 (4, 14)	
Age of onset:		
Mean ± SD	21.1±9.5	
Median	19 (15, 27)	

Comparative studies:

Patients with RP were significantly younger regarding age of disease onset (*p*-value=0.008), they also showed higher frequency of thrombosis (*p*-value=0.004), secondary vasculitis (*p*-value <0.001), digital gangrene (*p*-value=0.003) and avascular necrosis (AVN) (*p*-value=0.001). They were also more frequently juvenile onset (*p*-value=0.002) and showed higher damage index (*p*-value=0.031). Further details of comparison of patients with RP and those without regarding clinical manifestations are shown in Table (2).

Patients with LR showed significantly higher frequency of thrombosis (*p*-value <0.001), secondary vasculitis (*p*-value=0.017), digital gangrene (*p*-value <0.001), neuropsychiatric manifestations (*p*-value <0.001) and musculo-skeletal manifestations (*p*-value=0.036). They were also more frequently juvenile onset (*p*-value=0.043) and showed higher damage index (*p*-value <0.001). Further details of comparison of patients with livedo and those without regarding clinical manifestations are shown in Table (2).

Regarding their immune profile, patients with RP showed statistically significant higher positivi-

ty of anti-phospholipid (APL) antibodies (*p*-value =0.005) in comparison to those without RP, similarly patients with LR showed statistically significanthigher positivity of APL antibodies (*p*-value = 0.013), additionally they showed statistically significant hypocomplementemia (*p*-value=0.039) as compared to those without LR. Details of such comparison are shown in Table (3).

On comparing our groups regarding comorbidities, dyslipidemia (*p*=0.011) and renal failure (*p*=0.040) were significantly more frequently detected in patients with LR compared to those without. Details of such comparison are shown in Table (4).

On comparing patients with LR and/or RP (group 1) to those without (group 2), patients in group (1) had significantly higher frequency of secondary vasculitis (*p*-value <0.001), neuropsychiatric manifestations (*p*-value=0.036), thrombosis (*p*-value =0.002) higher SLICC (*p*-value=0.018), and more frequent APL antibodies (*p*-value <0.001). Details are shown in Table (5).

Table (2): Clinical characteristics of the studied patients.

Items	Patients without Livedo (No=406)	Those with Livedo (No=16)	*p*-value	Patients without Raynaud's (No=335)	Patients with Raynaud's (No=87)	*p*-value
Age of onset [median (IQR)] (MW)	19 (15, 27)	15 (13.4, 19.5)	0.130	20 (15, 27)	16 (14, 22)	0.008*
Constitutional manifestations	298 (73.4%)	13 (81.3%)	0.484	242 (72.2%)	69 (79.3%)	0.182
Thrombosis	57 (14.0%)	8 (50.0%)	<0.001*	43 (12.8%)	22 (25.3%)	0.004*
Secondary vasculitis (125)	116 (28.6%)	9 (56.3%)	0.017*	82 (24.5%)	43 (49.4%)	<0.001*
Digital gangrene (FET)	9 (2.2%)	3 (18.8%)	<0.001*	4 (1.2%)	8 (9.2%)	0.003*
Pulmonary hypertension	41 (10.1%)	3 (18.8%)	0.267	36 (10.7%)	8 (9.2%)	0.673
Alveolar hemorrhage	6 (1.5%)	0 (0.0%)	0.624	5 (1.5%)	1 (1.1%)	>0.999
Cardiac manifestations	92 (22.7%)	7 (43.8%)	0.051	81 (24.2%)	18 (20.7%)	0.494
Proteinuria	272 (67.0%)	11 (68.8%)	0.844	222 (66.3%)	61 (70.1%)	0.496
Neuropsychiatric	144 (35.5%)	13 (81.3%)	<0.001*	117 (34.9%)	40 (46.0%)	0.057
GIT (FET)	68 (16.7%)	3 (18.8%)	0.834	58 (17.3%)	13 (14.9%)	0.598
Musculoskeletal	362 (89.2%)	11 (68.8%)	0.036*	292 (87.2%)	81 (93.1%)	0.123
Retinal vasculitis (FET)	13 (3.2%)	1 (6.3%)	0.504	9 (2.7%)	5 (5.7%)	0.156
Optic atrophy (FET)	1 (0.2%)	1 (6.3%)	0.074	1 (0.3%)	1 (1.1%)	0.303
Pericarditis	54 (13.3%)	3 (18.8%)	0.532	47 (14.0%)	10 (11.5%)	0.538
AVN	33 (8.1%)	3 (18.8%)	0.136	21 (6.3%)	15 (17.2%)	0.001*
Sex:						
Female	361 (88.9%)	15 (93.8%)	0.543	295 (88.1%)	81 (93.1%)	0.179
Male	45 (11.1%)	1 (6.3%)		40 (11.9%)	6 (6.9%)	
Onset:						
Juvenile	175 (43.1%)	11 (68.8%)	0.043*	135 (40.3%)	51 (58.6%)	0.002*
Adult	231 (56.9%)	5 (31.3%)		200 (59.7%)	36 (41.4%)	
SLEDAI [median (IQR)] (MW)	2 (0, 6)	2 (0, 6)	0.117	2 (0, 6)	1 (0, 4)	0.117
SLICC-DI [median (IQR)] (MW)	1 (0, 2)	3 (1, 5.8)	<0.001*	1 (0, 2)	1 (1, 3)	0.031*

GIT : Gastrointestinal tract.

AVN: Avascular necrosis.

MW: Mann Whitney U non parametric test.

FET: Fisher exact test.

Table (3): Immune profilein the studied patients.

Labs	Patients without Livedo (No=406)	Those with Livedo (No=16)	*p*-value	Patients without Raynaud's (No=335)	Patients with Raynaud's (No=87)	*p*-value
ANA positivity (no=272)	389 (97.0%)	16 (100.0%)	0.483	321 (97.3%)	84 (96.6%)	0.720
Anti-ds DNA antibodies positivity (no=272)	260 (70.5%)	12 (85.7%)	0.217	247 (71.3%)	53 (69.7%)	0.783
Hypocomplementemia (no=117)	109 (29.7%)	8 (57.1%)	0.039*	90 (29.8%)	27 (34.2%)	0.453
APL antibody positivity	112 (37.6%)	11 (68.8%)	0.013*	86 (35.1%)	37 (53.1%)	0.005*

ANA: Antinuclear antibody.

Anti-ds DNA: Anti-double-stranded deoxyribonucleic acid antibody.

APL: Anti-phospholipidic.

Table (4): Associated co-morbidities of our studied patients.

Comorbidities	Patients without Livedo (No=406)	Those with Livedo (No=16)	*p*-value	Patients without Raynaud's (No=335)	Patients with Raynaud's (No=87)	*p*-value
HTN (no=146)	138 (34.0%)	8 (50.0%)	0.187	115 (34.3%)	31 (35.6%)	0.820
Dyslipidemia (no=140)	130 (32%)	10 (62.5%)	0.011*	109 (32.5%)	31 (35.6%)	0.610
DM (FET)	29 (7.1%)	2 (12.5%)	0.420	24 (7.2%)	7 (8.0%)	0.779
Thyroid	17 (4.2%)	0 (0.0%)	0.403	13 (3.9%)	4 (4.6%)	0.762
Malignancy (FET)	1 (0.2%)	0 (0.0%)	0.842	1 (0.3%)	0 (0.0%)	0.611
Renal Failure (FET)	24 (5.9%)	3 (18.8%)	0.040*	23 (6.9%)	4 (4.6%)	0.441
Cirrhosis (FET)	4 (1.0%)	0 (0.0%)	0.690	4 (1.2%)	0 (0.0%)	0.306
Osteoporosis (no=61)	56 (15.1%)	5 (33.3%)	0.058	43 (14.1%)	18 (22%)	0.391

FET: Fisher exact test.

Table (5): Comparison between patients with Livedo and/or Raynaud's and patients without regarding different patient characteristics.

Items	Patients without Livedo and Raynaud's (No=332)	Patients with Livedo and/or Raynaud's (No=90)	*p*-value
Secondary vasculitis	81 (24.4%)	44 (48.9%)	<0.001*
Cardiac manifestation	80 (24.1%)	19 (21.1%)	0.553
Pulmonary manifestation	171 (51.5%)	53 (58.9%)	0.213
Neuropsychiatric	115 (34.6%)	42 (46.7%)	0.036*
Retinal vasculitis	9 (2.7%)	5 (5.6%)	0.181
SLEDAI [median (IQR)] (MW)	2 (0, 6)	1 (0, 4)	0.251
SLICC-DI [median (IQR)] (MW)	1 (0, 2)	1 (0, 3)	0.018*
Hypocomplementemia	89 (26.8%)	29 (32.2%)	0.310
ANA positivity	318 (97.2%)	87 (96.7%)	0.727
Ant-DNA positivity	216 (71.1%)	56 (70.9%)	0.977
APL antibody positivity	84 (34.7%)	39 (54.2%)	0.003*
Thrombosis	42 (12.7%)	23 (25.6%)	0.002*
Mortality	40 (12.0%)	7 (7.8%)	0.253

MW: Mann Whitney U non parametric test.

Discussion

Mucocutaneous manifestations may occur in more than 80% of patients with SLE *[18]*. Their presence early in the course of the disease may facilitate early diagnosis and subsequently early management *[19]*, furthermore, in addition to their diagnostic importance, some points to their prognostic value *[4]*. It was reported that cutaneous small vessel vasculitis was associated with both mild and severe disease manifestations and that RP, is one of the predictors of the development of cutaneous small vessel vasculitis *[20]*.

In the present study RP was detected in 87 patients (20.6%), while LR was present in 16 out of 422 patients (3.8%). RP prevalence is comparable to other studies (18-46%) *[11,21]*, while regarding LR prevalence, it was reported that LR prevalence is variable in lupus patients, and they found that it is 15% in SLE with APs, 4% in SLE with positive APL, and 0% in SLE without APS and negative APL profile *[22]*. It is also to be considered that LR was found to be less frequent in JSLE compared to ASLE *[23,24]*, and that JSLE patients represents (44.1%) of our cohort. In our study, patients with RP had significantly younger age of disease onset (p-value=0.008). This is in contrast to the study of Heimovski and colleagues 2015, where results suggested that patients with RP experienced disease onset at older ages *[12]*.

In the current study, patients having RP or LR showed significantly higher frequency of secondary vasculitis. Previous studies showed a significant association of vasculitis with LR and RP *[1,25,26,27]*. Also, patients having RP or LR showed significantly higher frequency of thrombosis and digital gangrene, Heimovski and colleagues, 2015 reported that although RP is caused by vasospasm of the small vessels and not by thrombosis, thrombotic events may complicate severe forms with sustained vasospasm *[12]*. Furthermore, LR which is a consequence of cutaneous blood flow disturbance, is one of the important extra-criteria manifestations of Antiphospholipid syndrome, which is one of the most important causes of thrombosis in lupus patients *[28]*, additionally a higher a-CL titers was found in patients with RP *[29]*.

LR was also associated with statistically significant hypocomplementemia which has been previously reported to be associated with cutaneous vasculitis *[30]*.

In the present study, RP but not LR was associated with higher frequency of AVN, previous studies have found RP & vasculitis to be among potential risk factors for development of AVN in SLE patients *[31,32]*. A significant association between thrombocytopenia and cardiac dysfunction, epilepsy, arthritis and LR was reported *[33]* further more they confirmed association of LR with neurological manifestations especially headache and stroke in lupus patients, all this may strengthen the concept that LR-APS patients may represent special subset of patients with higher risk of thrombosis, which is associated with a higher frequency of damage and lower survival *[33]*. Additionally, it was found that-LR is a common finding in patients with cholesterol embolization syndrome, which is increasingly recognized cause of renal insufficiency and organ damage *[34]*. Finally, we can conclude that the association between LR, RP and SLICC damage index may be considered expected, as LR and or RP were associated with many important components in damage index as thrombosis, neurological manifestations and digital gangrene, further more RP was associated with AVN and LR was associated with renal failure. The association with APL may further explain the extra damage, as SLE with APL is usually associated with more damage.

In our opinion RP and LR are easily detected cutaneous findings that may have prognostic values, as they may be associated with more damage in lupus patients. Thus patients with RP and LR could be considered as unique phenotype of lupus patients that may require more frequent follow-up and special care. However further studies, including larger number of SLE patients with RP and LR will be needed to confirm our findings.

Limitations: The small number of patients with LR included in this study.

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القيمة التنبئية للتزرق الشبكى ولظاهرة رينود فى مرضى الذئبة الحمراء

الذئبة الحمراء هى مرض التهابى مناعى ذاتى مزمن متعدد الأجهزة. يعتبر الجلد ثانى أكثر الأعضاء إصابة فى مرضى الذئبة. يعتبر التزرق الشبكى وظاهرة رينود من المظاهر التغيرات الجلدية غير المحددة التى تحدث فى مرض الذئبة الحمراء.

تهدف هذه الدراسة إلى دراسة مدى تكرار ظاهرة رينود والتزرق الشبكى لدى مرضى الذئبة الحمراء وعلاقتها بنتائج المرض. فى الدراسة الحالية قمنا بتحليل السجلات الطبية بأثر رجعى لمجموع ٤٢٢ مريضًا بمرض الذئبة الحمراء، وفقًا لوجود أو عدم وجود االتزرق الشبكى وظاهرة رينود. وتوصلنا أن مرضى الذئبة الذين يعانون من رينود و/أو التزرق الشبكى قد يترافقون مع نتائج مرضية أسوأ ومؤشر ضرر أعلى.