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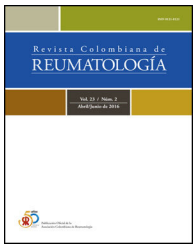

Original Investigation

Capillaroscopic abnormalities in systemic lupus erythematosus and its association with clinical manifestation

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ABSTRACT

Introduction: Capillaroscopy is a non-invasive tool used to evaluate microcirculation and determine whether a Raynaud's phenomenon is primary or secondary. Capillaroscopic changes are well-described in systemic sclerosis; however, these alterations have been less studied in other autoimmune diseases.

Objective: The aim of this study is to determine videocapillaroscopic alterations in lupus, and its association with clinical manifestations.

Materials and methods: A cross-sectional study with analytical intention was performed. Videocapillaroscopy and medical evaluations were performed on 76 patients with lupus, according to SLICC 2012 classificatory criteria, from January to June 2019. Chi^2, Fisher, and Mann–Whitney *U* tests were used to evaluate association, and the prevalence ratios (PR) were determined. A multivariate analysis was performed.

Results: Seventy-one (93.4%) of the patients were female with a median age of 33.5 years (interquartile range [IQR]: 27–44.8); the median lupus duration was 84 months (IQR: 30–168). The main clinical manifestations were articular, cutaneous, hematological, and Raynaud's phenomenon. A non-specific pattern was found in 43 patients (56.6%), and a systemic sclerosis-like pattern was found in 7 patients (9.2%). In bivariate and multivariate analyses, Raynaud episodes occurring more than once a week (PR 1.24; 95% CI: 1.13–1.33) were more frequent in patients with a sclerosis-like or a non-specific pattern.

Conclusion: Lupus patients frequently have videocapillaroscopic alterations with non-specific and systemic sclerosis like patterns, which are more common in patients with Raynaud's phenomenon that occurs more than once a week. Due to the study's design, it is impossible to determine causality.

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Anormalidades capilaroscópicas en el lupus eritematoso sistémico y su asociación con manifestación clínicas

Palabras clave:
Angioscopia microscópica
Lupus eritematoso sistémico
Fenómeno de Raynaud
Hipertensión pulmonar
Índice de severidad de la enfermedad

RESUMEN

Introducción: La capilaroscopia es una herramienta no invasiva utilizada para evaluar la microcirculación y determinar si el fenómeno de Raynaud es primario o secundario. Los cambios capilaroscópicos están bien descritos en la esclerosis sistémica, sin embargo, estas alteraciones se han estudiado menos en otras enfermedades autoinmunes.
Objetivo: El objetivo de este estudio es determinar las alteraciones videocapilaroscópicas en el lupus y su asociación con manifestaciones clínicas.
Materiales y métodos: Estudio transversal con intención analítica. Se realizó videocapilaroscopia y evaluación médica a 76 pacientes con lupus de enero a junio del 2019. Se utilizaron las pruebas U de Mann-Whitney, Chi cuadrado y Fisher para evaluar la asociación, y se determinaron las razones de prevalencia (PR). Se realizó un análisis multivariado.
Resultados: Setenta y un (93,4%) pacientes eran mujeres, con edad media de 33,5 años (rango intercuartil [RIQ]: 27-44,8); la mediana de duración del lupus fue de 84 meses (RIQ: 30-168). Las principales manifestaciones clínicas fueron articulares, cutáneas, hematológicas y el fenómeno de Raynaud. Se encontró un patrón no específico en 43 pacientes (56,6%) y un patrón similar a la esclerosis sistémica en siete pacientes (9,2%). En los análisis bivariados y multivariados, los episodios de Raynaud que ocurren más de una vez por semana (PR 1,24; IC 95%: 1,13-1,33) fueron más frecuentes en pacientes con un patrón de esclerosis no específico.
Conclusión: Los pacientes con lupus con frecuencia tienen alteraciones videocapilaroscópicas con patrones no específicos, que son más comunes en pacientes con fenómeno de Raynaud que ocurre más de una vez por semana.

Introduction

Systemic lupus erythematosus (SLE) is a disease that affects the immune system and is characterized by a broad spectrum of laboratory and multisystemic clinical manifestations. It has a variable course, with cycles of remission – activity. Delays in diagnosis can lead to accumulated damage, decreased quality of life, and increased mortality.[1] The annual incidence of SLE in the United States ranges from two to 7.6 per 1000 inhabitants/year. The prevalence varies widely between 19 and 159 per 1000 inhabitants, depending on the definition, race, genetic history, age, and sex. In Colombia, the Integral Information System of Social Protection statistics reports a prevalence of 87.7 per 1000 inhabitants. It is much more common in women than men, with a 9:1 ratio, but it has a more aggressive behavior in men.[2]

Endothelial cell damage has been found within the pathophysiology of SLE, which is mediated by homocysteine and pro-inflammatory cytokines, such as IFNα, which affect endothelial function and decrease the availability of precursor cells to repair endothelial injuries.[3] These alterations have led some authors to propose capillaroscopy as a helpful tool in SLE.[4–8] Capillaroscopy is a non-invasive technique that enables the study of microcirculation; it can determine whether a Raynaud phenomenon is primary or secondary due to systemic sclerosis, and view capillary damage.[9] Although the capillaries can be evaluated by other techniques, such as dermatoscopy, ophthalmoscope, light microscope (stereoscope), and USB microscope, only digital videocapillaroscopy makes it possible to dynamically assess microvascular abnormalities with adequate optical magnification (200×), as well as the computerized study of the different capillary parameters, generating quantitative and semiquantitative estimates and allowing more accurate and standardized approaches.[10,11]

In a systematic review published by Cutolo et al.[12] in 2018 on capillaroscopy, 40 articles were found on capillaroscopy in SLE. Most of these studies were carried out in European populations, an important aspect because this population has a more benign clinical behavior than Latin American patients. These differences can be seen in cohorts such as the Latin American Group for the study of lupus (GLADEL)[13] and the cohort of Lupus in Minorities: Nature vs. Nurture (LUMINA)[14] not only in the clinical course but also in the genetic, environmental, and socioeconomic aspects. Furthermore, in the previous review, only nine studies were performed using a videocapillaroscopy device. Therefore, it is necessary to find out the videocapillaroscopic changes of SLE in the Colombian population and whether there is an association with specific manifestations of the disease, and thus generate hypotheses for new follow-up studies to understand if the videocapillaroscopic alterations are present before or after the manifestation.

Materials and methods

A cross-sectional study with analytical intention was performed on patients diagnosed with SLE by a rheumatologist and who met the 2012 American College of Rheumatology classification criteria.[15] The patients were summoned to the videocapillaroscopy service of a reference center in Medellin, Colombia, between January and June 2019.

The sample was calculated with a 90% confidence level and a 10% margin of error, for a proportion of abnormalities of 50%, because of the great variability found in previous studies, in which abnormalities range from 6 to 80% of the population. This provided a total sample of 68 patients. The variables considered were demographic, clinical, laboratory, MEX SLEDAI for measurement disease activity, the index developed by the members of the Systemic Lupus International Collaborating Clinics (SLICC), and the standardized capillaroscopic variables to perform a semi-quantitative measurement.[16]

Patients had to be over 18 years of age, have SLE diagnosis by a rheumatologist, a previous medical record, and sign the informed consent. Patients with an uncertain diagnosis, incomplete medical records (loss of more than 20% of the variables), manipulation of the cuticle 15 days before videocapillaroscopy, or those allergic to almonds (since almond oil was the immersion oil used to evaluate the microcirculation) were excluded.

The patients were summoned to complete a questionnaire covering demographic and clinical characteristics. Also, the medical record was reviewed. All subjects underwent video capillaroscopy with Optilia equipment, using a 200× lens and the OptiPix software (Optilia Instruments; Sollentuna, Sweden, Universidad Pontificia Bolivariana, 2014). The procedure was performed following international standards: evaluation of the index fingers to the little finger of both hands, in a room at room temperature (26–32 °C), without having smoked or taken coffee within 4 h before the study. Four photos were taken per finger, and the first row of capillary handles was evaluated.[17] The videocapillaroscopy and its interpretation were performed by two rheumatologists certified by the Capillaroscopy Service of the University of Genova (Italy). They have a kappa coefficient of 0.84 (95% CI 0.66–1.0) and more than five years' experience in the field.

In the capillaroscopic evaluation, we used the semi-quantitative method described by Cutolo et al.[16] and the Smith et al. update[18] to analyze the images. This article defines the non-specific pattern as density minor to seven capillaries, dimensions between 20 and 50 μm, hemorrhages, and presence of abnormal capillary morphology defined as any form different from "hairpin," crossing shape, or tortuous shape. We used the definition of systemic sclerosis like pattern as described by Lambova.[19] We did not take the definition of systemic sclerosis pattern because our patients did not have systemic sclerosis, and the more accurate term was systemic sclerosis like. We used the three screening questions described by Wigley and Flavahan[20] to define Raynaud's phenomenon. The avascular area definition was taken from the capillaroscopy atlas of Cutolo,[16] defined as the absence of two capillaries in each dermal papillae or the presence of an area of 500 μm devoid of such.

An electronic form was designed using the Google forms tool, and a pilot test was carried out on the first five consecutive patients to estimate the time required per patient to obtain the information and make the necessary adjustments, thus guaranteeing process reliability. Once the information collection was completed, it was exported to a Microsoft Excel® 2010 licensed spreadsheet and later to SPSS 21 version licensed from CES University.

Some strategies were used to limit bias; in a single-center study, there was a selection bias due to a single recruitment source. To control this, patients were recruited from local patients' associations and asked other colleagues for referrals. The patients' medical history was reviewed to avoid memory bias regarding antibody type and clinical manifestations, and a physical examination was performed. Cases with a different time of evolution of the disease were included to avoid bias in the disease's duration. Observer bias was avoided by performing standardized video capillaroscopy by trained personnel. To prevent spurious associations, some variables of the health status of the patients that could cause confusion were measured, including jobs that could produce microtrauma in the fingers.

Analysis of the quantitative variables was performed according to the report of the Kolmogorov–Smirnov normality test. Since the distribution was not normal, the median and interquartile range (RIQ) were reported. For the analysis of the qualitative variables, absolute and relative frequencies were reported.

The epidemiological measure prevalence ratio (PR) with its confidence interval was reported for the bivariate analysis. According to the nature of the analyzed variables, the statistical test was a Chi^2 of independence or Fisher or a U of Mann–Whitney. We performed a multivariate model, with an initial analysis of collinearity, inputting in the model the variables that met the Hosmer–Lemeshow criteria (p-value < 0.25) and the confounding variables hypertension, having another autoimmune disease, and the SLICC and MEX SLEDAI scores. Statistical significance was considered with a p-value <0.05.

Ethical considerations

This research was considered a minimal risk and obtained authorization from the ethics committee of the participating institution. All patients signed the informed consent to participate in the study.

Results

During the first semester of 2019, 76 patients with SLE were evaluated. 93.4% ($n = 71$) were women, with a median age of 33.5 years (RIQ 27–44.8). Some of the factors that could alter the video capillaroscopic pattern, such as the use of percussion vibration instruments at work, playing the guitar, and smoking, were currently found in 3.9% ($n = 3$), 1.3% ($n = 1$), and 3.9% ($n = 3$) respectively. The most common clinical manifestation was arthritis (85.5%), followed by cutaneous (76.3%). Antinuclear antibodies (ANAS) were positive in 96.8% ($n = 61/63$); no data were obtained in 13 records (17.1%). The main ANAS pattern was speckled (50.8%, 32/63 patients) followed by homoge-

Table 1 – Demographic and clinical characteristics of 76 patients with SLE evaluated in a videocapillaroscopy service in Medellín, during the first half of 2019.

Characteristic	n	%
Female	71	93.4
Age (years)*	33.5	27–44.75
Race		
Mestizo	58	76.3
White	18	23.7
*Time of disease evolution in months**	84	30–168
12 months or less	10	13.2
More than 12 months	66	86.8
Current or past clinical manifestation		
Joint involvement	65	85.5
Skin involvement	58	76.3
Hematological involvement	54	71.1
Raynaud's phenomenon	39	51.3
Lupus nephritis	36	47.4
Serositis	25	32.9
Central neurological involvement	10	13.2
Vasculitis	11	14.5
Peripheral neurological involvement	6	7.9
Myositis	7	9.2
Pulmonary hypertension	5	6.6
Alveolar hemorrhage	5	6.6
Interstitial lung disease	4	5.3
Digital ulcers	4	5.3
Gastrointestinal involvement	4	5.3
Myocarditis	3	3.9
Valvular disease	2	2.6
Diabetes		
Yes	3	3.9
No	73	96.1
Arterial hypertension		
Yes	23	30.3
No	53	69.7
Other autoimmune disease associated		
Yes	14	18.4
No	62	81.6
Hospitalized patient	7	9.2
Patient with disease activity	15	19.7
SLICC ≥ 1	33	43.4

* Values expressed as median and interquartile range (IQR).

Table 2 – Videocapillaroscopic characteristics in 76 patients with SLE evaluated in a videocapillaroscopy service in Medellín, during the first semester of 2019.

	n	%
Characteristic		
Density ≥ 7	74	97.4
Abnormal morphology	31	40.8
Hemorrhages	16	21.1
Capillaries 20–50 μm	33	43.4
Giant capillaries	4	5.2
Capillaroscopic pattern		
Normal	26	34.2
Non-specific	43	56.6
Systemic sclerosis like	7	9.2

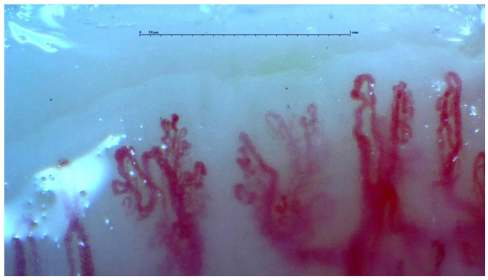

Photo 1 – Non-specific pattern. Patient with LES, ANAS 1:320 homogeneous pattern, without ENAS data, with Raynaud phenomenon, without cutaneous injuries. Videocapillaroscopy 200×, with non-specific pattern, given by capillaries greater than 20 μm and multiple hemorrhages.

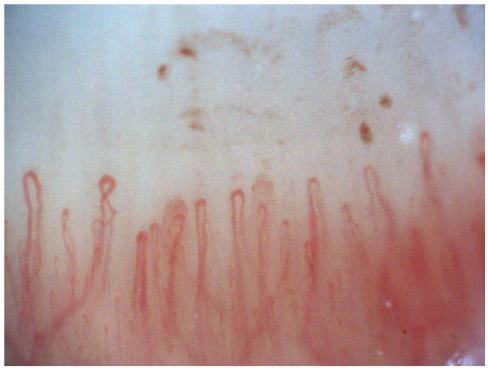

Photo 2 – Sclerosis systemic like pattern. Patient with LES, ANAS 1:160 speckled pattern, RNP >200, Sm 109, Raynaud phenomenon. No digital ulcer. Videocapillaroscopy 200×, with sclerosis systemic like pattern, given by decrease in the number of capillaries, capillaries greater than 20 μm and presence of arborescent capillaries.

neous (25.4%, 16/63 patients). Other patterns found were cytoplasmic, granular, and nucleolar. The core extractable antibodies (ENAS) were obtained in 65 patients and were positive in 63.1% ($n = 41/65$), the most common were Sm and RNP which were positive in 63.4% ($n = 26/41$) and 65.9% ($n = 27/41$) respectively. Table 1 shows the demographic and clinical characteristics; patients can have more than one clinical manifestation, so the total sum of the manifestations is greater than 100.

Table 2 describes the videocapillaroscopic characteristics of patients with SLE, and the final pattern. Normal patterns were found in 26 patients (34.2%). Of those with a systemic sclerosis like pattern, 85.7% ($n = 6$) had a positive ENA RNP. Photo 1 shows an example of non-specific pattern and Photo 2 shows an example of sclerosis systemic like pattern.

When each of the components of the videocapillaroscopy was analyzed, it was found that patients with more than one Raynaud's attack per week had more giant capillaries: 12.9% vs. 0% ($p = 0.02$); and patients with pulmonary hypertension had more giant capillaries: 40% vs. 2.8% ($p = 0.02$), and more avascular areas: 40% vs. 4.2% ($p = 0.032$).

Due to the scarce patients found with systemic sclerosis like patterns, we merged the capillaroscopic patterns that were non-specific and systemic sclerosis like in one category

Table 3 – A multivariate model of videocapillaroscopy of 76 patients with SLE evaluated in a videocapillaroscopy service in Medellín, during the first semester of 2019.

Characteristic	Bivariate analysis			Multivariate analysis		
	p-Value	PR	CI	*p*-Value	PR	CI
Female sex	0.159	0.900	0.821–0.987	0.092	1.161	0.976–1.381
Do not have peripheral neurologic manifestation	0.089	0.880	0.794–0.975	0.635	0.962	0.820–1.129
Actual cutaneous manifestation	0.051	2.773	0.888–8.658	0.058	0.915	0.835–1.003
>1 Raynaud attack per week	0.001	6.240	1.598–24.371	0.001	1.224	1.126–1.331
Myositis	0.222	0.390	0.094–1.328	0.073	1.123	0.989–1.275
Serositis	0.076	0.563	0.301–1.053	0.013	1.107	1.022–1.119

that we named abnormal pattern. This allows us to analyze the associations better.

In the bivariate analysis, an evaluation of abnormal pattern (non-specific and systemic sclerosis like) vs. normal pattern was made. The findings indicate that females had a negative association with an abnormal pattern, PR 0.71 (CI 0.45–1.14). Do not have peripheral neurologic involvement also had a negative association, PR 0.88 (CI 0.79–0.97), and the Raynaud phenomenon with more than one attack per week was associated with an abnormal pattern, PR 6.24 (CI 1.59–24.37).

In the multivariate analysis, the variables: Raynaud's phenomenon, more than one attack per week, and not having peripheral neurologic involvement, were included, because they had a significant *p* value. The variables sex, current skin involvement, myositis, and serositis, were also included because they met the Hosmer–Lemeshow criterion. In the multivariate analysis, we found that having more than one attack per week had a $p < 0.05$, a narrower confidence interval, and was associated with an abnormal pattern. Table 3 summarizes the results of bivariate and multivariate analysis.

Discussion

In this study, 76 patients diagnosed with SLE were analyzed who had undergone videocapillaroscopy to define the association between the different known patterns and clinical manifestations. The population was similar to that of other studies, with a predominance of young women.[4,21–23] A non-specific pattern was found in 43 patients (56.6%) and systemic sclerosis like pattern in seven patients (9.2%), 26 patients (34.2%) being normal then. Those data differ from those published by Zhao et al.,[24] who only found a normal pattern in 15.3% of their patients, and Pavlov-Dolijanovic et al. in whom 72% of their patients had a normal pattern.[7] However, there are few studies in SLE that evaluate the capillaroscopic pattern itself, and most of them assess the alterations in each of the capillaroscopy subitems. In addition, the changes to the definitions over time make comparisons difficult.

In this study, we did not find an association between capillaroscopic abnormalities and disease activity, as evidenced in other studies[8,23–25]; this could be secondary to the low number of patients with activity (19.7%) within the analyzed sample.

The increased frequency of non-specific and systemic sclerosis like patterns in patients with more than one episode per week of Raynaud's phenomenon is secondary because this is considered a marker of endothelial dysfunction. Recurrent episodes of vasospasm can lead to microinfarctions and the development of digital ulcers or gangrene.[25] Previous studies have shown an increase in the apical diameter of the capillaries, being more conclusive when Raynaud's is considered frequent at more than once per week.[7,26,27] It is necessary to evaluate whether these findings are permanent or predict other clinical manifestations. Pulmonary hypertension is among the manifestations of vascular involvement. However, it only occurs in 2.2% of patients according to the GLADEL cohort,[28] which is consistent with this study and may explain an increase in the frequency of giant capillaries. Possibly, this alteration would have had a stronger association if the number of patients with this manifestation had been greater, as demonstrated in the Donnarumma study, where capillaroscopy was suggested as a screening method for pulmonary hypertension.[6]

The findings of the semi-quantitative videocapillaroscopy score, indicate that patients with SLE and vascular alterations have more microbleeds, consistent with previous studies.[7,29,30] In future studies, it is necessary to evaluate whether these are a marker of disease activity or are associated with specific manifestations.

RNP was positive in 85.7% of our patients with a systemic sclerosis like pattern; some years ago, it was proposed that 'scleroderma-like' capillaroscopic changes in SLE are a hint of subclinical overlap with systemic sclerosis associated with anti-RNP antibody.[6,31,32] Although later studies found no association with RNP, concluding that the presence of cutaneous digital lesions hinted at such capillaroscopic pattern. These studies had difficulties in follow-up or measuring titles of RNP in all the patients, which could limit its interpretation.[33,34]

This study has several limitations: the absence of complete laboratory data on the profile of antiphospholipid syndrome, and all the ENAS to establish associations, more so when it is evident that 85.7% of patients with a systemic sclerosis like pattern had positive RNP. Its cross-sectional design cannot assess temporality; whether the capillaroscopy alterations occurred first or resulted from repetitive microvascular damage cannot be determined. Also, the small number of patients with lupus activity hinders the study's ability to evaluate the activity's effect on capillaroscopic alterations.

Despite its limitations, this study's main strength is that it was carried out using standard definitions. Given the large number of contradictory results from the use of different definitions in capillaroscopy, the results of the multicenter study carried out by the microcirculation group of the European League against rheumatism will help establish the final usefulness of this tool in SLE.[35]

Conclusions

Patients with SLE can present videocapillaroscopic alterations, especially those with Raynaud's phenomenon. These findings could be helpful for their follow-up. However, it is crucial to determine if these changes appear before the manifestation and are predictors or are a consequence thereof. Likewise, it should be studied whether there is a change in time depending on the treatment or the degree of the disease's activity.

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Conflicts of interest

The authors declare that they have no known competing financial interests.

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