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Correlation of nailfold capillaroscopy findings with history of digital ulcer on same finger: results of SCLEROCAP study

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Abstract

Systemic sclerosis may be complicated by digital ulcers. Nailfold capillaroscopy on one finger might reflect an increased risk of digital ulcer (DU). In the present study we studied the correlations between a history of ulcer and capillary findings on the finger.

Method: This study is part of Sclerocap, a multicenter study aiming at validating prospectively the prognostic value of Maricq's and Cutolo's capillaroscopic classifications during a three-year longitudinal follow-up. A history of past or present digital ulcer was recorded at inclusion and nailfold capillaroscopy was performed. Elementary findings as well as Cutolo and Maricq's classifications were assessed.

Results. 387 patients were included in Sclerocap (327 females, 60 males) and 3096 fingers were examined by capillaroscopy at inclusion: 316 fingers (10%) belonging to 113 patients had a history of DU. Late Cutolo's stage was statistically correlated with a history of DU, both by univariate: OR 2.08 [1.09-3.96] and multivariate analysis: OR 1.97 [1.06-3.63]. Among the elemental abnormalities, only edema and decreased capillary density were correlated with a history of DU by multivariate analysis: respectively OR 1.92 [1.17-3.16] and 0.65 [0.49-0.85].

Conclusion: This cross-sectional study in a large cohort of patients with systemic sclerosis shows a correlation between a history of digital ulcer and edema, a decrease in capillary density and the late stage in Cutolo's classification. The extent of capillary abnormalities on one finger is associated with a history of local digital ulcer. Capillaroscopy might be used to predict the risk of DU but these results need first to be confirmed by prospective studies.

Key words

Capillaroscopy, systemic sclerosis, digital ulcer, finger ischemia, microcirculation

Key messages

1 Capillaroscopy findings on finger are correlated with history of digital ulcer in systemic sclerosis

2 history of SSc-related DU correlates with edema, decrease in density and late stage in capillaroscopy

Systemic sclerosis (SSc) is an auto-immune connective tissue disease with the early involvement of microcirculation. It may result in life-threatening complications such as pulmonary, cardiac and renal complications. Digital ulcers (DU) occur in 36 to 58% of SSc patients, are recurrent, painful and severely disabling and may be complicated by infection and gangrene leading to amputation (1-5). Diffuse skin involvement and the presence of anti-topo-isomerase I auto-antibodies (Ab) in the blood are predictive of DU (6). Nailfold videocapillaroscopy (NVC) is a non-invasive means of exploring microcirculation that reveals specific abnormalities and is useful to establish the diagnosis of SSc. These abnormalities are now included in the EULAR/ACR criteria for SSc (7). NVC has also been proposed to classify patients with SSc according to the risk of declaring complications (8-10). A recent DELPHI consensus about the definition of the accurate items to use for capillaroscopy in clinical research was to use Cutolo's classification (11). A dramatic decrease in capillary density predicts a poor prognosis, while a high number of giant capillaries and hemorrhages predicts a better prognosis, according to Maricq's and Cutolo's classifications (7-9). Intercapillary distance, which reflects capillary loss (12), and the complex CSURI NVC score, have also been found to be associated with the risk of DU (13). Laser speckle analysis showed a significant decrease of perfusion in the periulcer area and an improvement with treatment, a confirmation of the direct role of local microcirculation on DU (14). NVC has also been used not only to predict the onset of SSc but also for the monitoring of treatment (15-16).

SCLEROCAP is a French multicenter prospective study with a three-year follow-up that is investigating the predictive potential of the NVC score in the evolution of SSc. We previously showed that patients at inclusion who had significant capillary loss in one of their eight examinable fingers (omitting the thumbs) according to Maricq's active and Cutolo's late stages had an increased risk of having more severe disease and having a history of DU. (17). It thus seemed useful to analyze the relationship between DU and capillaroscopy at

finger level and not only for one patient to better understand the pathophysiology of DU in SSc and to identify fingers at risk in a given patient. The objective of the study was to determine whether there is an association between the presence of active or past digital ulcers and the Maricq and Cutolo classifications at the level of each finger. The secondary objective was to determine whether there is an association between the presence of active or past digital ulcers and the factors of the Maricq and Cutolo classifications, individually and per finger. Here we present the results.

Methods

Study design

SCLEROCAP is a multicenter observational prospective study aiming at validating prospectively the prognostic value of Maricq's and Cutolo's capillaroscopic classifications in patients with SSc during a three-year longitudinal follow-up (17). One of the secondary objectives was to study the predictive value of capillaroscopic classifications for DU. SCLEROCAP was designed in compliance with good clinical practices and the Declaration of Helsinki. Formal ethical committee approval was obtained on March 7, 2014. The patients gave formal written consent. The study ended in August 2018 after three years of follow-up. The methods were described in detail previously (18) and are briefly summarized here.

Setting and participants

A total of 387 consecutive patients were included from four different types of medical departments (vascular medicine, rheumatology, internal medicine, and dermatology) in 10 French hospitals. Inclusion criteria were age \geq 18 years and having SSc according to LeRoy and Medsger's definition in order to include patients with early SSc and those with SSc but without skin sclerosis (19). These criteria were used instead of the ACR/EULAR criteria because the study was designed before the publication of these criteria and because many

patients seen early by vascular physicians do not have skin thickening yet. Non-inclusion criteria were having had other associated connective tissue disease or severe complications of SSc at inclusion, such as renal episode, pulmonary hypertension or respiratory insufficiency.

Study procedures

Demographic data, general medical history, subtype of SSc estimated with Rodnan score, and clinical and biological SSc characteristics were collected at inclusion. Nailfold capillaroscopic data and finger systolic pressure measurements were obtained at inclusion, and at each annual visit during the three years of SCLEROCAP follow-up. Investigators evaluated the existence of current or past fingertip ulcers on each finger. Past ulcers were attested by the presence of a scar or necrosis on the fingertip. Standardized methodology for wide-field capillaroscopy was used in all sites as reported before (18). A standardized report was used to read capillaroscopy for each of the eight examinable fingers, providing information about quantitative and qualitative abnormalities. Maricq's and Cutolo's scoring systems were used to define a progression stage, globally and for each finger (9,19). Maricq's stages were the following: "slow" corresponding to exceedingly enlarged capillaries with no or few avascular areas, and "active" corresponding to the absence of enlarged capillaries with moderate-to-extensive avascular areas. Cutolo's stages were divided into three groups: "early", with few megacapillaries, few hemorrhages, and relatively preserved capillaries in number and distribution; "active", with a medium loss of capillaries with few avascular areas, regular megacapillaries and hemorrhages (fig 1a), no or few ramified capillaries and slightly disorganized capillary architecture; and "late", corresponding to a significant loss of capillaries with large highly disorganized avascular areas, erratic enlargement and a frequent ramified or bushy structure, no or few megacapillaries and the absence of hemorrhage (fig 1b). Normal capillaroscopies were also considered in the analysis.

Images were collected in each center and anonymized for blinded review by another investigator and, in the event of discordance, by a third one to define a global capillaroscopic pattern for each patient. For finger-by-finger analysis, the classification was established by the first investigator who performed the examination. The same wide-field video-capillaroscopy device (50 to 100 magnification, Capview HD Perimed, France) was used in all centers and for all measures.

Number of subjects required

Enrollment was calculated to meet the primary objective of the study, i.e. to evaluate the prognostic performance of capillaroscopic phenotype in predicting three-year severe complications in SSc. The study size was calculated according to the association between capillaroscopic phenotype at inclusion and the presence of severe complications at three years.

The assumption of the incidence of severe complications at three years in all patients (good and poor prognosis combined) comparable to that observed in the ERAMS study (a multicentric prospective study that demonstrated that arterial stiffness predicted the risk of severe complications in SSc) was estimated at 22.5 %. The study size was estimated by making different assumptions of association, using the odds ratio ranging from 2 to 4, with a first-species risk set at 5% and a power of 90%. Considering these different estimates and the recruitment capacities of this study, a minimum of 350 patients was required to meet the primary objective.

Statistical analysis

Categorical variables were described in terms of numbers and percentages. Quantitative variables were described in terms of number, mean, standard deviation, median, minimum, maximum, first and third quartile. Ulcer presence was a binary variable (presence/absence) analyzed for each finger. Active and past ulcers were analyzed together. We performed univariate and multivariate mixed logistic regression models. The statistical level for the models was the finger. We performed a univariate analysis to determine the existence of an

association between the presence of active or past digital ulcers and the Maricq and Cutolo classifications as a whole. We combined the normal, early and active stages of Cutolo's classification into a single stage to have only an early stage and a late stage, which is more clinically informative. Our aim was to study late stage as predictive of DU and the combination of normal, early and active stages simplified and increased the power of analysis and seemed logical since there was no clinical difference between the patients normal, early and active stages. We added the variables predictive of ulceration in the literature to our multivariate models, i.e., age, Rodnan stage, hemoglobin level and duration of disease. We added a random effect on patient to account for the correlation between fingers belonging to the same individual. We performed a univariate analysis to determine the existence of an association between the presence of active or past digital ulcers and the constituent factors of the Maricq and Cutolo classifications taken individually. Then, we selected factors with a $p < 0.05$ for the multivariate model as well as some variables from the literature (age, Rodnan score, hemoglobin level, and disease duration). A p-value of less than 0.05 was considered statistically significant. R studio software version 1.2.5033 was used to compute the statistical analysis.

Results

The SCLEROCAP study included 387 patients (327 females, 60 males, mean age 63 ± 14). Of these patients, 59 (15.2%) had an unspecific or normal capillaroscopic pattern at inclusion. The 328 patients with abnormalities were divided into 211 (64.3%) slow and 117 (35.7%) active patterns according to Maricq's classification and classified as 87 (26.5%) early, 145 (44%) active and 96 (29%) late patterns according to Cutolo's classification. Details of patients were previously published (18, table III). SSc subtype was limited in 88 patients (23%), cutaneous limited in 243 patients (63%) and cutaneous diffuse in 56 patients (15%). Mean duration of SSc was 12.29 ± 7.48 years. Anticentromere antibodies were found in 223 patients (58%) and anti-topo-isomerase I in 69 patients (18%).

Among the patients included, 3096 fingers were examined by capillaroscopy at inclusion: 316 fingers (10%) belonging to 113 patients had a history of active DU or pitting scar. Table I shows Maricq's and Cutolo's classifications for the fingers according to a history of past or present ulcer or not. Active Maricq's stage was associated, although not statistically significant in multivariate analysis, with a history of DU on the considered finger: OR 1.66 [0.88-3.12] (Table II). Late Cutolo's stage was statistically correlated with a history of DU, both by univariate: OR 2.08 [1.09-3.96] and multivariate analysis: OR 1.97 [1.06-3.63] (Table III) in which we adjusted on Rodnan's score, age, duration of illness and hemoglobin level. Among the elemental abnormalities, only edema and decreased capillary density ($\leq 7/\text{mm}$) were correlated with a history of digital ulcer, and these variables were still significant in the multivariate analysis adjusted on Rodnan's score, age, duration of illness and hemoglobin level: respectively OR 1.92 [1.17-3.16] and 0.65 [0.49-0.85] (table IV).

Discussion

SCLEROCAP is the first study to investigate the relationship between a history of DU and the NVC pattern finger by finger and not by patient. Multivariate analysis revealed an association between NVC classifications and a history of DU at the finger level for Cutolo's late stage: OR 2.08 [1.09-3.93]. The same association was also found for Maricq's active stage, although not significantly. By multivariate analysis the association between Cutolo's late stage and active ulcer or pitting scar on the considered finger was still significant and the only other factor associated with DU was Rodnan's skin score. Similar results were found for a decrease in capillary density that was also associated with DU and still significantly so in multivariate analysis: OR 0.65 [0.49-0.85]. These results are the first to report a correlation between late Cutolo's stage or capillary density and an history of DU at the finger level. The correlation between Rodnan's skin score and DU is not surprising since DU are more frequent in diffuse SSc than in SSc with limited skin involvement as found in DUO study (6). Microcirculatory modifications observed by NVC seem to be related to the risk of local ulcer, suggesting that the extent of capillary loss might be directly implicated in the pathogenesis of DU. These

findings are in agreement with previous results. Smith reported that NVC predicted the risk of DU after a follow-up of 18 to 24 months, with an odds ratio of 16 for Cutolo's late stage (20).

Even when capillary loss was not included into one of both staging systems, it was still correlated with a history of DU at finger level. However, this parameter is significant only when measured as the capillary density in the middle of the finger but not when measured as the maximal density. Smith found that capillary density had a 72% sensitivity and specificity for predicting DU (21). Horimoto performed a cross-sectional study among 70 SSc patients, of whom 14 had active DU (22). In another study by Leroy, the only NVC parameter to correlate with the presence of DU was also capillary density (21). Sebastiani developed a score, the CSURI, consisting of MxD/N^2 (m=number of giant capillaries, D= maximal capillary diameter, N= number of capillaries) that accounts for the proportion of giant capillaries among the total number of capillaries (23, 24). It was associated with DU in a multicenter study of 120 SSc patients of whom 35 had DU: 33 of the 35 patients with DU had a CSURI >2.94 versus only 12 of the 85 patients with no DU (15). However, the CSURI is complex to calculate and its association with DU is affected by bosentan treatment (25). All these previous studies addressed the relationship between DU and capillaroscopy in a given patient but not finger by finger.

The relationship between edema and history of DU is more difficult to interpret. Capillary edema might simply result from local inflammation of the fingertip, where an active ulcer is present.

The main limitation of SCLEROCAP is its cross-sectional design. This limitation will be resolved by the prospective part of the study whose results are forthcoming. Its strengths are its multicenter design and blinded reading of NVC from two to three experienced investigators at patient level, not finger level. This is important since inter-observer agreement regarding NVC classifications and elementary capillary data is questionable. In

intra-class correlation was about 0.6 for Maricq's and Cutolo's classifications as well as for capillary density in a previous report from the SCLEROCAP team (18).

NVC might be used not only for the diagnosis of SSc as currently used but also to assess prognosis, especially the risk of DU (27,28). The findings of SCLEROCAP confirm the previously suggested association between capillary loss, either isolated or integrated into Cutolo's late stage, with a history of DU. Capillary loss seems to be the most important capillary factor to predict the risk of DU, even though its predictive value remains to be confirmed by the longitudinal part of the SCLEROCAP study that will be the only way to assess the interest of NVC to predict DU. For this reason, no clear algorithm may be proposed for a specific daily management of SSc patients. However our results are the first to show a direct correlation of capillary loss or late Cutolo's stage with DU at the finger level, suggesting its pathophysiological role in DU and giving hope of specific measures if the present data from SCLEROCAP are confirmed by longitudinal results.

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Legend of figure 1

Figure 1a : NVC pattern of a patient free from DU (Cutolo's active stage, Maricq's slow stage)

Figure 1b : NVC pattern of patient with DU (Cutolo's late stage, Maricq's active stage)

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Table I. Classification of capillaroscopic patterns according to Maricq and Cutolo in fingers of sclerodermic patients with or without digital ulcers

	No digital ulcer present or past N= 2780 fingers	Past or present digital ulcer N=316 fingers
Maricq's classification (764 not classifiable)		
normal	162(8%)	7(3%)
slow	1282(61%)	120(46%)
active	649(31%)	132(51%)
Cutolo's classification (774 not classable)		
normal	157(8%)	7(3%)
early	543(26%)	32(12%)
active	841(41%)	101(39%)
late	525(25%)	116(45%)

Table II Correlation between Maricq's active stage and active ulcer or pitting scar on finger

Univariate analysis		
Variable	Odds ratio [95%CI]	P value
Active stage	1.66 [0.88-3.12]	0.12
Multivariate analysis		
Active stage	1.52 [0.83-2.78]	0.17
Rodnan skin score	2.61 [1.63-4.2]	<0.01
Age years	0.68 [0.42-1.08]	0.10
Duration of SSc years	1.20 [0.76-1.88]	0.43
Hemoglobin rate g/dl	0.22 [0.03-1.51]	0.12

Table III Correlation between Cutolo's late stage and active ulcer or pitting scar on finger

Univariate analysis		
Variable	Odds ratio [95%CI]	P value
Late stage	2.08 [1.09-3.96]	0.03
Multivariate analysis		
Late stage	1.97 [1.06-3.63]	0.03
Rodnan skin score	2.59 [1.63-4.11]	<0.01
Age years	0.67 [0.42-1.06]	0.09
Duration of SSc years	1.19 [0.76-1.85]	0.44
Hemoglobin rate g/dl	0.25 [0.04-1.67]	0.15

Table IV: Correlation between elementary abnormalities and active digital ulcer or pitting scar

Univariate analysis		
Variable	Odds ratio [95%CI]	P value
1 giant capillary	0.93	0.31
>1 giant capillary	0.17	
Moderate disorganization	1.34 [0.74-2.42]	0.53
Severe disorganization	1.48 [0.72-3.04]	
1 avascular area	1.31 [0.8-2.14]	0.53
>1 avascular area	1.31 [0.7-2.47]	
Rare dystrophic capillaries	0.85 [0.52-1.37]	0.69
Frequent dystrophic capillaries	0.65 [0.34-1.65]	
Rare hemorrhages	1.04 [0.63-1.73]	0.44
Frequent hemorrhages	0.69 [0.36-1.32]	
Edema	1.92 [1.17-3.16]	<0.01
<i>Capillary density</i>		
Maximal finger density	0.98 [0.76-1.26]	0.88
Middle of finger	0.65 [0.49-0.85]	<0.01
Multivariate analysis		
Capillary density middle of finger	0.65 [0.5-0.85]	<0.01
Rodnan's skin score	2.89 [1.82-4.58]	<0.01
age	0.71 [0.45-1.12]	0.14
Duration of SSc	1.14 [0.73-1.78]	0.57
Hemoglobin rate	0.23 [0.06-1.6]	0.14