From VEDOSS to established systemic sclerosis diagnosis according to ACR/EULAR 2013 classification criteria: a French-Italian capillaroscopic survey

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ABSTRACT

Objective. *Nailfold capillaroscopy (NC) shows microcirculatory abnormalities in systemic sclerosis (SSc). The inclusion of NC specific abnormalities increases the sensitivity of both 2013 ACR/EULAR and VEDOSS (Very Early Diagnosis of Systemic Sclerosis) classification criteria. We aimed to detect NC features able to predict progression toward established SSc in VEDOSS patients.*

Methods. *Sixty-six VEDOSS patients were enrolled. They had a clinical follow-up and underwent NC once a year, considering morphological parameters, appropriate pattern and semiquantitative rating scale.*

Results. *In a mean follow-up time of 31 months, 21 patients progressed into SSc (P = Progressors), while 45 were "Non Progressor" (NP). Comparing NC basal features of both groups, significantly larger loop diameter and apex width, higher haemorrhage and NC scores were found in P respect to NP patients. When comparing NC features of P patients who progressed within one year (FP = Fast progressor), loop diameter and apex width were significantly higher compared to all VEDOSS subjects. Each unit increase of apex width was associated with an increasing risk of 1% for developing SSc and the cut-off value of 103 µm showed a positive predictive value of 56% and a negative predictive value of 71%.*

Conclusion. *We describe NC findings in VEDOSS patients, identifying those suggesting a progression into established disease. These findings must be regarded as possible predictive risk factor to develop SSc and can also be of relevance in the detection of those cases with a faster development. Thus NC seems to have a diagnostic and prognostic role in VEDOSS cases.*

Introduction

Nailfold capillaroscopy (NC) is a safe and non-invasive technique able to show microcirculatory abnormalities in systemic sclerosis (SSc) patients. It is the more reliable method for morphological assessment of nutritive capillaries in the nailfold area, becoming a diagnostic and prognostic tool in case of scleroderma pattern (1, 2). The main indication for NC in rheumatology is the differential diagnosis of primary and secondary Raynaud's phenomenon (RP), the latter being the hallmark of both SSc and Very Early Diagnosis of SSc (VEDOSS). In fact NC is nowadays regarded as the favourite confirmatory diagnostic tool (together with specific autoantibodies) to diagnose a patient as having very early SSc with a high probability (3). This evidence has been confirmed by a study showing that, in patients with SSc-specific autoantibodies at baseline, Raynaud's phenomenon and abnormal NC, there was a 79.5% probability of developing established SSc after up to 9 years of observation (4). On the contrary, the absence of a scleroderma pattern at NC is very valuable in the exclusion of SSc in unselected patients with Raynaud's phenomenon (4, 5).

Moreover, the inclusion of NC specific abnormalities has increased the sensitivity of the classification criteria, becoming both a minor criterion in 2013 ACR/EULAR SSc Classification Criteria (6) and a major criterion with high clinical relevance for VEDOSS (3).

The VEDOSS project, indicating some signs and symptoms as "red flags" for suspicion of SSc, identifies those patients in the very early phase of the disease enabling a "window of opportunity" to act with strategic treatments to prevent or at least to slow the progression of the disease (7).

NC has a well-known role in the diagnostic process of early scleroderma, thus it should not be considered optional for the rheumatologists, also looking at NC with the aim of using it as a prognostic marker. Indeed, as recently attested in two independent cohorts, NC changes may be predictive of novel future severe organ involvement in SSc (8, 9).

In this context, given the promises of early classification of SSc patients and the large use of NC both in VEDOSS and in SSc patients, we aimed to detect any NC characteristics in VEDOSS patients which could predict progression toward established SSc. Such NC features, behaving as predictive risk factors, were obtained by monitoring a group of VEDOSS patients longitudinally and including a centralised reading of NC. This observational study attempted to predict what the outcome of SSc development is to be. Therefore, the baseline NC abnormalities of VEDOSS patients developing established SSc at follow-up were accurately compared with those of VEDOSS patients not progressing into SSc, to determine any possible relationship between the instrumental findings and clinical manifestations.

Materials and methods

Sixty-six consecutive VEDOSS patients (M/F=4/62; mean age=53.3yrs; mean duration of Raynaud's phenomenon=148months) fulfilling the VEDOSS criteria (3) were enrolled in two academic centres. The study was approved by both local Ethical Committees of Policlinico Umberto I in Rome, Italy (Protocol n°227/12) and of Comité de Protection des Personnes Ile de France 3, France. The patients' written consent was obtained according to the Declaration of Helsinki. All subjects had a regular follow-up in order to select those cases who would develop established SSc according to 2013 ACR/EULAR criteria (6). All patients underwent NC regularly once a year during the follow-up. In each patient, the nailfolds of all fingers except thumbs were examined after a drop of immersion oil was placed on the nailfold bed to improve resolution. NC was performed according to the standard method (10). Both centres used a 200x magnification and all the images were made anonymous and double blindly examined by the same expert investigators (MV and VR) on the same device. The following morphological parameters were separately considered, according to previous classifications (11):

a) loop diameter: the diameter at the apex of a capillary loop;
b) apex width: the maximum open space measured in the apex of a capillary; (measuring the wider loop for each finger and then the mean value of the three wider loops among the eight fingers in each patient).
c) capillary distribution (regular, slightly irregular, disorganised);
d) capillary density (normal ≥9 capillaries, or reduced, <9 capillaries per linear millimeter),
e) capillary enlargement/megacapillaries (enlarged=20-50 μm, giant>50 μm);
f) presence of haemorrhages (score ≤1 if present in ≤2 fingers; score >1 if present in >2 fingers).

Moreover, a semi-quantitative rating scale to score the main capillary abnormalities was also adopted, according to previous studies (12-14): score 0=no change; 1=few (<4) alterations; 2=some (between 4 and 6) alterations; 3=frequent (6 or more) alterations per linear millimeter. The morphological parameters and the mean score value for each subject were obtained from the analysis of four consecutive fields (one linear millimeter for each one), in each digit; the average score values from all digits were added together, and the final value divided for all fingers. The NC results were also distributed into a proper pattern when appropriate: early, active and late (13). The clinical and laboratory data obtained during the follow-up were recorded at the time of each NC exam.

Statistical analysis

All analysis were performed using SPSS for Windows (Statistical Package for the Social Sciences, Version 24). The qualitative variables were described as frequencies and percentage, while the continuous once as medians and interquartile range.

The examined outcome was progression or not towards SSc.

Univariate statistical analysis of categorical parameters was performed by the Pearson's Chi-square test or Fisher's exact test while comparisons between continuous variables were tested by Mann-Whitney test for unpaired samples.

A multivariate logistic regression model was performed to study the outcome progression or not towards SSc. The inclusion of any covariate in the model was decided on the basis of the univariate analysis (p-value <0.05). Stepwise with backward elimination of non-significant variables (probability to entry p<0.05) was subsequently used to generate a minimal model. The goodness of fit for the model was assessed with Hosmer and Lemeshow' s test for the logistic model (15). Significance threshold was set at p<0.05 (two-tailed) for all analyses. Area under the receiver characteristic curve (ROC-AUC) was used to evaluate the diagnostic utility of capillaroscopic features.

Reliability among operators (MV and VR) was assessed by both Bland-Altman analysis and intra-class correlation coefficient (ICC).

Results

Twenty-five patients were enrolled in the French academic centre, while 41 patients were enrolled in the Italian one (M/F=4/62; mean age=53.3yrs; mean duration of Raynaud's phenomenon=148 months). All patients were diagnosed as VEDOSS at the first visit, while nobody satisfied 2013 ACR/EULAR criteria for SSc.

In a mean follow-up time of 31 months (range 6–60 months), 21 patients progressed into definite SSc (P=Progressors). The remaining 45 VEDOSS patients were named "Non Progressor" (NP). Table I shows the main features of the two groups.

When comparing NC features at baseline in the two groups (P *vs*. NP patients), we found several significant differences: a larger loop diameter (median values 65μm *vs*. 41.5μm; p=0.006) and a larger apex width (median values 128μm *vs*. 73.5μm; p=0.002) in P patients respect to NP patients. A significantly higher score for haemorrhages (47% *vs*. 21% respectively, p=0.033)

Table I. Main clinical, demographic and laboratory features of VEDOSS Progressor (P) and Non Progressor (NP) patients at baseline.

Main clinical, demographic and laboratory parameters	P patients (n=21)	NP patients (n=45)	*p*-value
Age (yrs) (range)	55.4 (27-77)	52.3 (24-70)	n.s.
Sex (M/F)	2/19	2/43	n.s.
Disease duration from 1st visit (months) (range)	50 (21-70)	45 (3-70)	n.s.
Duration of Raynaud's phenomenon (months) (range)	158 (33-606)	143 (1-444)	n.s.
ANA positive n (%)	2 (9)	16 (35)	0.03
Anti-Topo I positive n (%)	5 (24)	3 (7)	0.09
ACA positive n (%)	14 (66)	23 (51)	n.s.
Any specific SSc Ab§ n (%)	19 (90)	26 (58)	0.01
Presence of teleangectasia§ n (%)	3 (14)	7 (15)	n.s.
Presence of puffy fingers§ n (%)	5 (24)	11 (24)	n.s.
Presence of abnormal NC§ n (%)	13 (62)	21 (47)	n.s.

§The contemporary presence of any of these items in the same subject did not allow to satisfy the 2013 ACR/EULAR classification.

Table II. Main NC features of VEDOSS Progressor (P) and Non Progressor (NP) patients at baseline.

NC PARAMETERS	P patients (n=21)	NP patients (n=45)	*p*-value
Loop diameter (μm) (median, IR)	65, 65	41.5, 37	0.006
Apex width (μm) (median, IR)	128, 117	73.5, 58	0.002
Capillary densityn pts (%)	Normal = 12 (57) Reduced = 9 (42)	Normal = 29 (69) Reduced = 16 (38)	n.s.
Capillary enlargement n pts (%)	Enlarged loops =10 (47) Giant loops = 10 (47)	Enlarged loops = 16 (38) Giant loops =17 (40)	n.s.
Haemorrahage score>1 n pts (%)	10 (47)	9 (21)	0.003
NC pattern n pts (%)	Not SSc related pattern=8 (38) Early =8 (38) Active = 4 (19) Late =1 (5)	Not SSc related pattern =23 (52) Early = 18 (41) Active =2 (4.5) Late =1 (2)	n.s. n.s. n.s. n.s.
NC Score>1 n pts (%)	13 (62)	11 (26)	0.006

*IR: interquartile range.

was found in P patients compared to NP patients. Moreover, a significantly higher NC score (>1) was present in P respect to NP subjects (62 *vs*. 26%, *p*=0.006). These results are shown in Table II. Logistic regression analysis showed that apex width was associated with disease progression (*p*=0.012; 1.01OR; 95% CI 1.002–1.019).

Figures 1 and 2 show NC pictures at baseline of a VEDOSS P patient and a VEDOSS NP patient, respectively.

Looking at the laboratory features, in our VEDOSS patients ANA positivity with no specificity for the so-called "specific SSc autoantibodies" was significantly more frequent in NP cases (9% in P *vs*. 35% in NP, *p*=0.03) while a positivity for any kind of "specific SSc autoantibodies" was significantly more frequent in P patients (90% in P *vs*. 58% in NP, *p*=0.01).

Among the 21 P patients, we investigated which of the 2013 ACR/EULAR classification criteria for SSc allowed the single VEDOSS patient to progress toward SSc. Puffy fingers were the most representative additional criteria, showed by 8 (42%) VEDOSS P patients, while teleangectasia was reported in 5 cases (26.5%). Sclerodactily, digital ulcers and abnormal specific NC findings were present in 2 patients (10.5%).

Finally, we analysed the time of VEDOSS diagnosis as well as the time of SSc diagnosis. In our 21 P patients we identified a group of "fast progressor" (FP), in which SSc diagnosis occurred within one year from VEDOSS diagnosis, and a second group, defined as "slow progressor" (SP), in which the diagnosis of SSc was made later than one year. According to that, we identified 7 FP and 14 SP. Although we could not find any significant differences in the basal NC parameters of the two groups, we detected a trend *versus* higher loop diameter and apex width in FP respect to SP. We then compared the clinical demographic features and the basal NC features of FP and all VEDOSS patients other than FP (SP+NP). Interestingly, we found a significantly higher loop diameter (127μm *vs*. 46μm; *p*=0.004) and a higher apex width (212μm *vs*. 87μm; *p*=0.004) in FP respect to all the other VEDOSS cases. These results are shown in Table III.

The multivariate logistic regression model for progression towards SSc showed that apex width was the strongest NC feature as independent risk factor for developing defined SSc (*p*=0.012 and OR 1.01 95% CI 1.002-1.012). This result is shown in Table IV.

The ROC-AUC analysis for the apex width feature between P and NP patients was 0.738 (SE=0.069, *p*=0.002, IC 95% 0.602-0.874). At a cut-off of 103 μm, corresponding to the greatest sum of specificity and sensitivity, both specificity and sensitivity were 71.4%. Positive predictive value (PPV) was 56% and negative predictive value (NPV) was 71% (Supplementary Fig. 1).

Bland-Altman analysis, to assess the reliability among operators, showed a mean difference of 2.2 μm (*p*=0.003, SD 23.037; upper level 47.352-lower level -42.952) (Supplementary Fig. 2).

Reliability between two different researchers (MV and VR) working independently was also calculated with the interclass correlation coefficient (ICC), by two-way random effect model. The SE in measuring capillary dimension was, for a width lower than 50 μm, of 7.3 μm (Supplementary Fig. 3).

Discussion

NC exam is of crucial value for the diagnosis and differentiation of primary and secondary Raynaud's phenomenon, whereas the appearance of abnormal capillaroscopic pattern, together

Fig. 1. Representative nailfold capillaroscopy at baseline of a VEDOSS patient still VEDOSS at the follow-up.

Fig. 2. Representative nailfold capillaroscopy at baseline of a VEDOSS patient progressing into SSc at the follow-up.

with the presence of SSc specific autoantibodies, inherits high positive predictive value for the development of scleroderma-related diseases. On the other hand, the absence of abnormal capillaroscopic findings can be regarded as a diagnostic criterion for primary Raynaud's phenomenon (4, 5, 16).

Besides, NC is a valuable tool for both very early SSc disease and for established SSc, due to its ability in showing pathognomonic microvascular alterations in these conditions. Its interpretation is crucial in the very early assessment of uncertain cases as some NC abnormalities, such as presence of giant capillaries or reduced number of capillaries, can give a remarkable push to the diagnosis (17-19). These NC abnormalities are indeed included in the major criteria for VEDOSS diagnosis, which has the aim of leading to an early treatment, which could in turn improve long-term outcome in SSc (20).

Moreover, the use of detailed NC parameters, may help to further make an early diagnosis of patients progression toward overt systemic disease. The present study describes for the first time in details the main NC findings in a group of VEDOSS patients. We compared some baseline NC features, such as loop diameter, apex width, capillary density, as well as the presence or absence of capillary enlargement/megacapillaries and haemorrhages, in two defined groups, one maintaining a stable VEDOSS diagnosis during time and the other progressing from VEDOSS to established SSc.

Higher loop diameter and apex width, presence and severity of haemorrhages as well as a higher NC score were significantly more frequent in those patients who progressed towards established SSc, the so-called VEDOSS P patients.

By definition, loop diameter is expressed as the diameter at the apex of a capillary loop while apex width is the maximum open space measured in the apex of a capillary (11). In 1986 both parameters were described higher in SSc patients than in healthy subjects (21). More recently, quantitative alterations of capillary diameter were described as having a predictive value for the development of SSc, thus they can be considered as forerunning NC abnormalities of the whole capillary enlargement, defining the so-called "giant" capillary (18). These parameters seem to be sensitive to identify scleroderma-related disorders and, in the same way, they can be taken in account for the detection of progression from an early connective tissue disease, such as our VEDOSS cohort, to an established connective tissue disease, such as our early SSc cohort.

The presence of haemorrhages, the other NC feature that was more frequently found in our P patients respect to the NP subjects, cannot be considered a specific SSc feature, but, together with other qualitative and quantitative abnormalities, including the length, the shape and the arrangement of capillaries, it has been previously included in a scoring system where the scleroderma pattern is expected (22).

Furthermore, the importance of NC scoring system was already assessed in established SSc, where the ability for a semi-quantitative rating scale to de-

Table III. Main clinical, demographical, laboratory and capillaroscopy features of VEDOSS Fast Progressor (FP), VEDOSS Slow Progressor (SP) and VEDOSS other than FP patients.

MAIN FEATURES	VEDOSS FP patients (n=7)	**VEDOSS SP patients (n=14)**	VEDOSS other than FP patients (n=59)
Age (Median, IR)	57, 12	**53, 20**	55, 20
Sex M/F)	2/5	**0/19**	0/59
Follow-up from first visit (months) (median. IR)	46, 30	**54, 13**	52, 25
Raynaud's duration (months) (median, IR)	108, 142	**157, 156**	108, 116
ACA positive n° pts (%)	5 (71)	**9 (64)**	32 (54)
Anti Topo I positive n° pts (%)	1 (14)	**3 (21)**	7 (12)
Teleangectasias n° pts (%)	2 (28)	**1 (7)**	8 (13)
Puffy fingers npts (%)	3 (43)	**2 (14)**	13 (22)
NVC Pattern n° pts (%)	Normal=3 (42)	**Normal=4 (31)**	Normal=28 (47)
	Early=3 (42)	**Early=5 (38)**	Early=22 (37)
	Active=0 (0)	**Active=4 (31)**	Active=7 (11)
	Late=1 (16)	**Late=0 (0)**	Late=1 (1)
Loop diameter (μm) (median, IR)	**127, 107***	**65, 40**	**46, 41***
Apex width (μm) (median, IR)	**212, 165***	**132, 89**	**87, 62***
Capillary density n° pts (%)	Normal=4 (57)	**Normal=7 (50)**	Normal=39 (66)
	Reduced=3 (43)	**Reduced=6 (43)**	Reduced=18 (30)
Capillary enlargement n° pts (%)	Enlarged loop=3 (43)	**Enlarged loop=6 (43)**	Enlarged loop=23 (39)
	Giant loop=4 (57)	**Giant loop=6 (43)**	Giant loop=22 (38)
Haemorrhages score>1 n° pts (%)	3 (43)	**2 (14)**	16 (28)
NC Score>1 n° pts (%)	3 (43)	**13 (92)**	21 (36)

IR: interquartile range; *p=0.004

Table IV. Multivariate logistic regression model for progression towards SSc.

Independent variables	Outcome progression towards SSc (yes/no)		
		95% CI	
	OR	Low	Up
Any SSc specific Ab			
absent	**1**		
present	**1.086**	**0.294**	**4.015**
NC Score:			
0-1	1		
2-3	1.254	0.256	6.149
Loop diameter	0.986	0.948	1.025
Haemorrahages:			
≤2 fingers	1		
>2 fingers	2.493	0.744	8.356
Apex width	**1.01**	**1.002**	**1.012***
Goodness of fit†		0.412	

*p=0.012. †Hosmer and Lemeshow's test.

tect the progression of microvascular damage during time was shown in 90 SSc patients (14). So, as this score was found to be a sensitive tool to monitor and quantify capillaroscopic changes in SSc patients, in our NC survey we adopted the same score for VEDOSS patients, comparing it in both VEDOSS patients who progressed to SSc at the follow-up as well as in those patients who did not progress. As demonstrated for established SSc, this tool proved to be sensitive to quantify and monitor the capillaroscopic features thus it might be used to survey the evolution of the vasculopathy in those cases presenting with undifferentiated disease. Interestingly, at basal NC exam, the score was found to be higher in those patients that later would have been shifted to a defined connective tissue disease, *i.e*. SSc.

Looking also at the laboratory features, in our VEDOSS patients ANA positivity with no specificity for the so-called "specific SSc autoantibodies" was significantly more frequent in NP patients while a positivity for any kind of "specific SSc autoantibodies" was significantly more frequent in those P cases. This finding suggests that the lack of autoantibodies such as ACA and anti-Topo I, should be taken into account for predicting a lack of progression to an established form of the disease, as already assessed by others (23), while their presence indicates a high probability of developing SSc. Moreover, we suggest that the contemporary detection of specific NC abnormalities with the presence of specific SSc autoantibodies could allow to increase their predictive value.

We tried to demonstrate that the NC exam may also be of help in identifying those patients that we defined as FP, where established SSc occurred within one year after the VEDOSS diagnosis. The lack of a significant difference in the comparison between FP and SP may depend on the small amount of our cohort, whereas the presence of larger loop diameter as well as of larger apex width seem to distinguish FP from both SP and NP groups taken together (VEDOSS patients other than FP; Table III). We thus wanted to underline that the existence of specific NC abnormal features at the time of VEDOSS diagnosis, should be regarded not only as a possible predictive risk factor for developing SSc, but it may also have a role in the detection of those cases with faster development.

Overall, the apex width revealed to be the strongest NC feature as independent risk factor for developing defined SSc. Indeed, in our cohort each unit increase of the apex width was found to be associated with an increasing risk of 1% for developing defined SSc as shown in Table IV. It was already shown that such parameter was a good distinctive factor among patients with different connective tissue diseases (21). The present study states its importance in the pro-

gression within the spectrum of scleroderma related disorders. As shown by AUC-ROC analysis, apex width measurement is a good test to distinguish P from NP patients. The 103 μm cut off allows to identify those subjects who will not progress towards established disease with a good probability, as assessed by a negative predictive value of 71%. This finding could allow a less close follow-up in these cases respect to those subjects showing an apex width higher than 103 μm, thus probably requiring deeper and closer investigations in order to detect an early progression to established disease.

The investigation for this parameter, easily obtained by all clinicians dealing with NC, could give an added value to the simple detection of "absence" or "presence" of enlarged loops. Indeed patients with enlarged-giant capillaries have a huge variability in the apex width (as we can see from the measurements of our cohort), and this could reflect distinct likelihood to develop a defined diagnosis of SSc. On the other hand, in our NP patients a consistently higher apex width is also shown, thus other risk factors are certainly to be taken in account for the development and progression of more severe form of the disease and they have to be further investigated. We also need to point out that the significant ORs obtained in our study were not statistically strong, thus some of the evaluated capillaroscopic parameters will certainly need to be adequately weighted in order to be correctly used for the clinical practice. Our longitudinal observational study, investigating for any possible changes with the purpose of identifying between various variables, was not probably able to detect certain causal relationships, and we must in any case take into consideration the low sample size of our cohort, involving only two academic centres, that needs to be implemented.

In conclusion, the biggest challenge in the fight against SSc is to find valid predictors of the disease in order to reduce the diagnostic delay. Our results point out that some specific NC abnormalities could be considered as *"red flags"* in the diagnostic repertoire of SSc, thus aiming not only for a well-defined diagnostic role of NC technique, but also underlying how it can be considered a sensible prognostic tool in those very early cases, where an early diagnosis can make the difference.

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