Scleroderma patients nailfold videocapillaroscopic patterns are associated with disease subset and disease severity

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Objective. To evaluate in a large group of scleroderma patients, the association of nailfold videocapillaroscopic patterns with both demographic and clinical features.

Methods. One hundred and three Italian patients (91 women and 12 men, mean age 54.3 years, median disease duration 7 yrs, 68 with limited and 35 with diffuse subset of disease), consecutively enrolled for the study, underwent nailfold videocapillaroscopy; the microvascular alterations were classified into three different patterns, early, active and late. The nailfold videocapillaroscopic patterns were correlated with such numerous clinical features as sex, age, disease duration, disease subset, disease activity, haematological data, involvement of skin, heart, lung and peripheral vessels.

Results. Nailfold videocapillaroscopic patterns were significantly associated with disease subsets (P = 0.018). Severity of skin, lung, heart and peripheral vascular involvement progressively increased across nailfold videocapillaroscopic patterns, from early to late pattern (P < 0.001 for cutaneous and peripheral vascular involvement; P = 0.003 and 0.002 for lung and heart involvement, respectively) as well as homocysteine plasma levels (P = 0.02). Patients with late pattern showed an increased risk to have an active disease [OR (odds ratio) 3.50; 95% CI (confidence interval) 1.31–9.39], to present digital ulcers (OR 5.74; 95% CI 2.08–15.89) and moderate to severe skin (OR 5.28; 95% CI 1.93–14.19), heart (OR 5.75; 95% CI 2.04–16.21) and lung involvement (OR 4.41; 95% CI 1.63–11.92).

Conclusions. Our study showed that scleroderma microangiopathy correlates with disease subset and severity of peripheral vascular, skin, heart and lung involvement; patients with late pattern showed an increased risk to have an active disease and to show a moderate/severe skin or visceral involvement compared to patients with early and active patterns. Therefore nailfold videocapillaroscopy, a simple, non-invasive and non-expensive investigation, is useful in staging scleroderma patients and also provides prognostic information.

Key words: Systemic sclerosis, nailfold videocapillaroscopy.

Introduction

Systemic sclerosis (SSc) is a multisystemic disorder of the connective tissue, characterized by microvascular damage with associated cutaneous and internal organ fibrosis and specific immunologic abnormalities. The clinical expression, severity and progression are rather heterogeneous; the disease may progress very slowly with no or mild visceral injury, whereas sometimes it dramatically evolves with early severe organ damage [1].

The pathogenesis of SSc is very complex and still largely unknown [2], but vascular perturbation is supposed to be a primary event, which may trigger and drive the fibrotic process. Several factors have been incriminated as possible triggering agents of vascular injury such as anti-endothelial antibodies [3], mechanisms of molecular mimicry [4], microchimerism phenomenon [5] and oxidative stress [6].

Histopathological hallmarks of SSc are perivascular infiltrates and a reduced capillary density, which precede the excessive accumulation of extracellular matrix proteins. The peculiar vascular involvement affects primarily small arteries and capillaries and causes reduced blood flow and tissue ischaemia, supporting the typical clinical manifestations of this unique autoimmune disorder.

Nailfold videocapillaroscopy (NVC) is a suitable tool for the assessment of SSc microvasculopathy [7–9]; the aim of the present study was to evaluate the association between nailfold videocapillaroscopic patterns with both clinical manifestations and haematological data in a large group of SSC patients.

Results

One hundred and three Italian patients (91 women and 12 men, mean age 54.3 ± 13.6 yrs, median disease duration 7 yrs with minimum–maximum range 1–46 yrs) were consecutively enrolled for the study between January and May 2006. All patients fulfilled the American College of Rheumatology criteria for the diagnosis of SSc [10]. The distinction between limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc) was made according to the criteria of LeRoy et al. [11]. All the patients gave written informed consent.

Patients were receiving a wide range of drugs, including vasodilators (101 patients), cyclophosphamide (9 patients), low dose prednisolone (<10 mg/day) (23 patients), aspirin (77 patients) and H2-receptor antagonists (83 patients).

Patients underwent examination and laboratory evaluation comprehensive of full blood count, ESR, renal and liver function indexes, fasting total homocysteine, antinuclear and anti-ENA antibody determination. Homocysteine levels were determined by high-performance liquid chromatography method with fluorescence detection [12] (normal <15 μmol/l). Anticentromere antibodies (ACA) were tested by indirect immunofluorescence on HEp-2 cells; anti-Sc170 antibodies were determined by ELISA.

Skin, vascular, lung and heart involvement. In all the patients skin involvement was assessed by the modified Rodnan skin score (mRSS) [13].

The same operator evaluated peripheral vascular involvement in agreement with criteria proposed by Medsger et al. [14].

All the patients underwent the following instrumental investigations: electrocardiogram; chest radiograph; pulmonary function test with diffusing capacity for carbon monoxide (DLCO) adjusted to haemoglobin; Doppler echocardiogram to evaluate left ventricular ejection fraction and to estimate pulmonary artery systolic pressure (sPAP); estimated sPAP was considered

Patients and methods

Study population

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Valentini et al. used geometric mean with 95% confidence interval (CI) and the transformation was performed for skewed variables, i.e. for homocysteine, 

Digital ulcers
Absent 77 (74.8)
FVCa 97.5
Chest radiography
Normal 81 (78.6)
Lung involvement
Absent 39 (37.9)
Peripheral vascular involvement
Absent 0
Lung involvement
Absent 39 (37.9)
Chest radiography
Normal 81 (78.6)
FVCa 97.5 ± 20.7
DLCOa 73 ± 20.9
Estimated sPAP Normal 83 (80.6)
Heart involvement
Absent 80 (77.7)
Medsger.

Sex Male 12 (11.7)
Female 91 (88.3)
SSc duration (years)b 7 (1–46)
Autoantibody pattern
ANA positivity (absent ACA and anti-Scl70) 55 (53.4)
Anti-Scl70 8 (7.8)
Homocysteine (\(\mu\)mol/l)c 11.8 (11.3–12.3)
Creatinine (mg/dl)a 0.79 ± 0.15
ESR (normal < 38 mm/h) Normal 76 (73.8)
High 27 (26.2)
mRSSa 11.4 (5.3)
Digital ulcers
Absent 77 (74.8)
Present 26 (25.2)
Peripheral vascular involvement
Absent 0
Mild 56 (54.4)
Moderate 22 (21.3)
Severe 25 (24.3)
Endstage 0
Lung involvement
Absent 39 (37.9)
Mild 27 (26.2)
Moderate 27 (26.2)
Severe 10 (9.7)
Endstage 0
Chest radiography
Normal 81 (78.6)
Interstitial lung disease 22 (21.4)
FVCa 97.5 ± 20.7
DLCOa 73 ± 20.9
Estimated sPAP Normal 83 (80.6)
Heart involvement
Absent 80 (77.7)
Mild 13 (12.6)
Moderate 8 (7.8)
Severe 2 (1.9)
Endstage 0

aValues expressed as mean ± s.d.
Values expressed as median with minimum–maximum range;
Values expressed as geometric mean with 95% confidence interval.
SSc, systemic sclerosis; lSSc, limited systemic sclerosis; dSSc, diffuse systemic sclerosis; NVC, nailfold videocapillaroscopy; ANA, antinuclear antibodies; ACA, anticitrullinated antibodies; Anti-Scl70, anti-Scl70 antibodies; ESR, erythrocyte sedimentation rate; mRSS, modified Rodnan skin score; FVC, forced vital capacity, % predicted; DLCO, diffusing capacity for carbon monoxide, % predicted; sPAP, pulmonary artery systolic pressure.

abnormal if \(\geq 35\) mmHg. Pulmonary and cardiac involvement was then evaluated based on a severity scale classification proposed by Medsger et al. [14]. The disease activity was assessed according to Valentini et al. [15].

The same operator, blind to clinical features, performed NVC and then evaluated based on a severity scale classification proposed by Cutolo et al. [16]. All investigations were performed at our hospital as part of the normal clinical evaluation of our SSc patients.

### Statistical analysis

All the analyses were performed with SPSS 13.0 statistical package (SPSS Inc., Chicago, IL, USA). Distribution of continuous variables in groups was expressed as mean ± s.d. Logarithmic transformation was performed for skewed variables, i.e. for homocysteine levels; therefore this variable was expressed as geometric mean with 95% confidence interval (CI) and the statistical differences concerning this parameter were also computed on the corresponding log-transformed values.

Quantitative data were assessed using the Student’s t-test or by ANOVA with Tukey’s post hoc comparison of the means and with polynomial contrasts analysis for linear trend, when indicated. Associations between qualitative variables were analysed with the chi-square (\(\chi^2\)) test, \(\chi^2\)-test for linear trend or Fisher exact-test, when indicated. To assess the association between NVC patterns and disease severity/organ involvement, odds ratio (OR) with 95% CI was also calculated by univariate logistic regression analysis, comparing patients with most severe pattern, the late pattern, with those with a less advanced pattern, i.e. early and active.

A value of \(P < 0.05\) was considered significant.

### Results

**Demographic and clinical characteristics of SSc patients**

The clinical characteristics of the 103 patients are summarized in Table 1.

**NVC pattern and clinical and laboratory phenotypes**

Thirty-six subjects (34.9%) had an early, 45 (43.7%) an active and 22 (21.4%) a late NVC pattern (Table 1). Table 2 shows the characteristics of patients on the basis of NVC pattern. Because of the low number of patients with a severe lung or heart involvement, we grouped them together with those of a moderate involvement.

NVC was significantly associated with SSc subset (\(P = 0.018\) by \(\chi^2\)-test), with early and active pattern more present among patients with lSSc, whereas the late pattern was more represented among patients with dSSc. Furthermore, subjects with late pattern were more represented among patients with active disease (OR 3.50; 95% CI 1.31–9.39).

There was a highly significant correlation of NVC pattern with skin involvement evaluated by mRSS, which progressively increased from early to late pattern (\(P < 0.001\) by ANOVA with polynomial contrasts analysis for linear trend). Considering a threshold level for the mRSS value, patients with late pattern had an increased risk of high mRSS, i.e. \(\geq 15\) (OR 5.28; 95% CI 1.93–14.49, \(P = 0.001\) by \(\chi^2\)-test).

The NVC pattern was highly significantly associated also with peripheral vascular involvement, as well as with digital ulcers (\(P < 0.001\) by \(\chi^2\)-test in both the analyses). The severity of vascular involvement progressively increased by the worsening of NVC pattern (\(\chi^2\) for linear trend = 19.298, \(P < 0.001\)) and patients with late pattern had a markedly increased risk of digital ulcers (OR 5.74; 95% CI 2.08–15.89, \(P < 0.001\) by \(\chi^2\)-test).

Similarly, across the NVC patterns—from early to late pattern, the severity of lung and of heart involvement progressively increased (\(\chi^2\) for linear trend = 8.673, \(P = 0.003\) and \(\chi^2\) for linear trend = 10.539, \(P = 0.002\), respectively). Patients with late pattern had an increased risk of moderate-severe lung involvement (OR 4.41; 95% CI 1.63–11.92), as well as of moderate-severe heart involvement (OR 5.75; 95% CI 2.04–16.21). Remarkably, we noted a significant trend of DLCO and forced vital capacity (FVC) levels across NVC patterns with the lowest values in the late pattern (\(P < 0.001\) and \(P = 0.010\) by ANOVA with polynomial contrasts analysis for linear trend, respectively). Furthermore, the late pattern was associated with an increased risk of interstitial lung disease (ILD) at chest radiography evaluation (OR 3.62; 95% CI 1.28–10.21).

Finally, we found a significant correlation between NVC pattern and plasma homocysteine concentration that progressively increased from the early to the late pattern (\(P = 0.020\) by ANOVA with polynomial contrasts analysis for linear trend).

No significant differences were found for the distribution of sex, age, disease duration, autoantibody profile, estimated sPAP,
haemoglobin, ESR and creatinine levels across NVC patterns; patients with late pattern tended to be older and to have a longer disease duration than those with early and active pattern although the difference did not reach a statistical significance.

Discussion

NVC is a simple, non-invasive and non-expensive investigation to assess capillary morphology; it has recently become an useful tool to diagnose and to follow-up microangiopathy in SSc patients. The classification of NVC abnormalities in three pattern—early, active and late—is relatively recent [16]; longitudinal studies will show if the three patterns are consecutive steps of the microvascular scleroderma damage.

At present, very few studies have correlated NVC patterns with demographic and clinical features of SSc patients. It has been reported that late NVC pattern is related to the age of patients and the disease duration [16, 17] as well as to the diffuse pattern of the disease [17]; moreover anti-Scl70 antibodies seem to be more frequent in patients with active and late patterns than in those with early NVC pattern [17]. The present study confirms a correlation between late NVC pattern and diffuse subset of disease; on the contrary no correlation has been found between NVC pattern and autoantibody profile. Patients with late NVC pattern were older and had a longer disease duration in comparison with patients with early and active pattern, but the difference did not reach statistical significance.

Differently from the previous studies, we have taken into consideration not only demographic features, autoantibody profile and SSc subset, but also clinical characteristics in relation to NVC pattern. We found out that the progression of skin, lung, heart and peripheral vascular involvement were all related to the worsening of microangiopathy as directly assessed by NVC. The correlation between NVC patterns and clinical manifestations of SSc may be due to common pathogenetic mechanisms, involving microvascularity at different levels and supports the concept that microvessel injury is the pivotal lesion of the complex pathogenesis of the disease. As expected, a very strong correlation was found between NVC pattern and digital ulcers, a severe manifestation of peripheral vascular involvement that heavily affects the quality of life.

Moreover, a strong correlation was observed between NVC pattern and DLCO either ILD or pulmonary hypertension impair DLCO; it was also suggested that isolated DLCO reduction might be indicative of lung microangiopathy [18]. A positive correlation between a component of DLCO—the diffusing capacity of the alveolocapillary membrane—and NVC abnormalities was previously reported [19].

Moreover, the disease activity was more frequent in patients with late NVC pattern than in patients with early-active NVC abnormalities.

The factors responsible for the different expression of the disease are largely unclear; it is known that the autoantibody profile is associated with disease subset, race, age and some clinical manifestations as digital ulcers, ILD and renal crisis [20]. Besides autoantibodies, several prognostic markers are available in order to predict survival and risk of visceral involvement. The extent of skin sclerosis is a relevant factor in the prognosis, having been associated with both severe morbidity and survival [21]. Serum levels of soluble adhesion molecules as VCAM-1 and E-selectin have been reported to be useful markers for monitoring clinical progression because they reflect disease severity [22]; then, serum levels of surfactant protein-D and KL-6 are associated to the risk of ILD [23, 24]. Nevertheless, to our knowledge, there is not any parameter correlating with the most relevant clinical features of SSc; some prognostic markers are useful to predict a single clinical expression of the disease [25]. Our study showed that NVC patterns were correlated with the principal SSc

Table 2. Clinical and laboratory characteristics on the basis of nailfold videocapillaroscopic pattern [data expressed as absolute number (%) unless otherwise indicated]

<table>
<thead>
<tr>
<th>NVC pattern</th>
<th>Early (n = 36)</th>
<th>Active (n = 45)</th>
<th>Late (n = 22)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)*</td>
<td>54.5 (13.4)</td>
<td>51 (14.1)</td>
<td>60.6 (11)</td>
<td>NS*</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5 (13.9)</td>
<td>3 (6.7)</td>
<td>4 (18.2)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>31 (86.1)</td>
<td>42 (93.3)</td>
<td>18 (81.8)</td>
<td></td>
</tr>
<tr>
<td>SSc duration (years)*</td>
<td>6 (1–41)</td>
<td>7 (1–17)</td>
<td>9 (1–46)</td>
<td>NS*</td>
</tr>
<tr>
<td>Subset</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISSc</td>
<td>27 (75.0)</td>
<td>32 (71.1)</td>
<td>9 (40.9)</td>
<td>0.018#</td>
</tr>
<tr>
<td>dSSc</td>
<td>9 (25.0)</td>
<td>13 (28.9)</td>
<td>13 (59.1)</td>
<td></td>
</tr>
<tr>
<td>Autoantibodies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ANA positivity</td>
<td>2 (5.6)</td>
<td>3 (6.7)</td>
<td>3 (13.6)</td>
<td>NS#</td>
</tr>
<tr>
<td>ACA</td>
<td>17 (47.2)</td>
<td>29 (64.4)</td>
<td>9 (40.9)</td>
<td></td>
</tr>
<tr>
<td>Anti-Scl70</td>
<td>17 (47.2)</td>
<td>13 (28.9)</td>
<td>10 (45.5)</td>
<td></td>
</tr>
<tr>
<td>Disease activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Present</td>
<td>7 (19.4)</td>
<td>11 (24.4)</td>
<td>11 (50.0)</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin (g/dl)*</td>
<td>13.3 (1)</td>
<td>34 (1.4)</td>
<td>15 (1.3)</td>
<td>NS*</td>
</tr>
<tr>
<td>Creatinine (mg/dl)*</td>
<td>0.79 (0.17)</td>
<td>0.77 (0.11)</td>
<td>0.83 (0.16)</td>
<td>NS*</td>
</tr>
<tr>
<td>Homocysteine (mmol/l)*</td>
<td>10.9 (10.4–11.5)</td>
<td>11.6 (11.0–12.2)</td>
<td>14.1 (12.5–15.9)</td>
<td>0.02*</td>
</tr>
<tr>
<td>ESR (normal ¼ 38 mm/h)</td>
<td>8 (22.2)</td>
<td>11 (24.4)</td>
<td>8 (36.4)</td>
<td></td>
</tr>
<tr>
<td>mRSS*</td>
<td>9.5 (4.7)</td>
<td>11.3 (5.5)</td>
<td>14.6 (5.7)</td>
<td>&lt;0.01*</td>
</tr>
<tr>
<td>Digital ulcers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Present           | 3 (8.3)       | 11 (24.4)      | 12 (54.5)    | <0.01#
| Peripheral vascular involvement | | | | |
| Moderate (grade 2) | 6 (16.7)   | 10 (22.2)      | 6 (27.9)     |       |
| Severe (grade 3)  | 2 (5.5)       | 11 (24.4)      | 12 (54.5)    |       |
| Pulmonary involvement | | | | |
| Absent (grade 0)  | 20 (55.6)     | 15 (33.3)      | 4 (18.2)     |       |
| Mild (grade 1)    | 28 (77.8)     | 24 (53.3)      | 4 (18.2)     |       |
| Moderate/Severe (grade 2–3) | 7 (19.4) | 16 (35.6) | 14 (63.6) |       |
| Chest radiography |               |                |              |       |
| Intestinal lung disease | 6 (16.7) | 17 (56.6) | 9 (40.9) | 0.04# |
| FVC*              | 101.5 (20.5)  | 99.3 (18.9)    | 86.9 (22.0)  | 0.01* |
| DLCO*             | 80.7 (16.6)   | 73.0 (21.9)    | 60.4 (20)    | <0.001*|
| High estimated sPAP | | | | |
| Moderate/Severe (grade 2–3) | 7 (19.4) | 7 (15.6) | 6 (27.3) | 0.002# |
| Heart involvement |               |                |              |       |
| Absent (grade 0)  | 32 (88.8)     | 37 (82.2)      | 11 (50.0)    |       |
| Mild (grade 1)    | 2 (5.6)       | 5 (11.1)       | 6 (27.3)     |       |
| Moderate/Severe (grade 2–3) | 2 (5.6) | 3 (6.7) | 5 (22.7) |       |

*Values expressed as mean (s.d.)
Values expressed as median with minimum–maximum range;
Values expressed as geometric mean with 95% confidence interval.
by ANOVA with polynomial contrasts for linear trend; # by chi-square for linear trend
NVC, nailfold videocapillaroscopy; SSc, systemic sclerosis; ISSc, limited systemic sclerosis; dSSc, diffuse systemic sclerosis; ANA, antinuclear antibodies; ACA, anticentromere antibodies; Anti-Scl70, anti-Scl70 antibodies; ESR, erythrocyte sedimentation rate; mRSS, modified Rodnan skin score; FVC, forced vital capacity; % predicted; DLCO, diffusion capacity for carbon monoxide, % predicted; sPAP, pulmonary artery systolic pressure.
manifestations and among these lung and heart involvement heavily weighs on mortality. Therefore, besides diagnostic role, NVC could acquire prognostic relevance in the global assessment of a single patient. Prospective studies are necessary to evaluate if NVC may influence therapeutic choices.

Concerning haematochemical parameters, we observed a progressive increase of homocysteine plasma levels from early to active and above all to late NVC pattern. In SSc, hyperhomocysteinaemia may represent an aggravating factor able to worsen the clinical course of the disease through the multiple pathways by which homocysteine alters the normal properties of vascular system; hyperhomocysteinaemia may further weigh on the SSc vascular dysfunction negatively interfering with the delicate regulation of vascular tone and may strengthen the injury caused by oxidative stress [26, 27].

In conclusion, our study showed that in SSc patients microvessel damage, as directly observed by NVC, is related to disease subset and disease severity affecting different sites as peripheral circulation, skin, heart and lung; patients with late pattern showed an increased risk to have an active disease and to be affected by a moderate/severe skin or visceral involvement, compared to patients with early and active patterns. Therefore, this simple tool helps to staging the patient affected by SSc and provides prognostic information.

The authors have declared no conflicts of interest.

Rheumatology key messages

- Scleroderma nailfold videocapillaroscopic patterns are related to disease subset and disease severity affecting different sites as peripheral circulation, skin, heart and lung.
- Scleroderma patients with late videocapillaroscopic pattern show an increased risk to have an active disease and to be affected by a moderate/severe skin or visceral involvement, compared with patients with early and active patterns.
- Nailfold videocapillaroscopy helps to staging the patient affected by systemic sclerosis and provides prognostic information.

References