Progression of Organ Involvement in Systemic Sclerosis Patients with Persistent "Late" Nailfold Capillaroscopic Pattern of Microangiopathy: A Prospective Study

To the Editor:

Systemic sclerosis (SSc) is a complex systemic connective tissue disease characterized by vasculopathy and progressive fibrosis of skin and internal organs.

Peripheral microangiopathy is a dynamic event characterized by progressive capillary loss. Its advanced stage is depicted by the "late" nailfold videocapillaroscopy (NVC) pattern of microvascular damage[1].

It has been reported that the decreased number of capillaries is associated with clinical subsets and the severity of SSc clinical complications[2,3,4,5].

We performed a study to assess, to our knowledge for the first time, possible correlations between absolute nailfold capillary number (CN) and organ involvement, in a cohort of SSc patients with the "Late" NVC pattern of microangiopathy diagnosed at baseline and during a followup of 5 years.

Twenty-three patients (22 women, mean age 64.30 ± 12.38 SD yrs, mean disease duration 7.74 ± 7.61 yrs, mean Raynaud phenomenon duration 17.87 ± 15.35 yrs) affected by SSc according to the American College of Rheumatology/European League Against Rheumatism criteria and displaying the "Late" NVC pattern at baseline were recruited and followed for 5 years[6].

All the patients gave written informed consent to enter the study. Ethics committee approval was not required for this type of noninvasive diagnostic tool (in accordance with the policy of our institution). During the followup, patients were receiving a wide range of drugs, including vasodilators (20 patients), cyclophosphamide (3), cyclosporine (8), methotrexate (4), mycophenolate (5), endothelin receptor antagonists (12), phosphodiesterase type 5 inhibitors (5), and aspirin (14).

To assess organ involvement, these procedures were performed annually: esophageal manometry, pulmonary function tests with DLCO, chest radiograph, lung computed tomography scan, electrocardiography, Doppler echocardiography with systolic pulmonary arterial pressure (PAP) measurement, and echo color Doppler with renal arterial resistive index (RI) measurement. Cardiac catheterization was performed in patients with Doppler echocardiography–estimated PAP > 40 mmHg to confirm the diagnosis of pulmonary arterial hypertension (PAH). Presence of new digital ulcers (DU) was assessed, as well as cumulative DU number per year[7]. Skin involvement was assessed by modified Rodnan skin score (mRSS) to classify patients with SSc as affected by either limited (lcSSc) or diffuse (dcSSc) cutaneous SSc[8].

NVC was performed to identify SSc patients with the "Late" pattern of microangiopathy, and to calculate the microangiopathy evolution score (MES)[9,10]. Absolute CN was also calculated according to standardized methods[10].

At baseline, 21 patients showed lcSSc (91%), 2 dcSSc (9%), 9 DU (39%), 17 esophageal dysmotility (74%), 11 interstitial lung disease (ILD; 48%), and 2 renal involvement (9%). No patients displayed PAH and/or heart involvement. In addition, 9 patients were found positive for anticentromere (ACA), 10 for anti–Scl-70, and 1 for anti-RNA polymerase III antibodies. At the end of 5 years of followup, 15 patients showed lcSSc (65%), 8 dcSSc (35%), 11 new DU (48%), 21 esophageal dysmotility (91%), 22 ILD (96%), and 5 renal involvement (22%). Finally, 2 patients showed PAH (9%) and 3 showed heart involvement (13%; Table 1).

A progressive statistically significant decrease in CN ($p < 0.0001$), forced vital capacity (FVC; $p = 0.0001$), and DLCO ($p < 0.0001$) values was observed from baseline to 5 years, as well as a progressive statistically significant increase in renal arterial RI ($p < 0.0001$), total DU ($p < 0.0001$), mRSS ($p = 0.0024$), and MES ($p = 0.01$; Friedman test; Table 2). PAP was found significantly increased only at 5 years compared to basal values ($p = 0.03$; Wilcoxon test).

Interestingly, the decrease in CN positively correlated over time with the worsening of FVC and DLCO values ($r = 1$, $p = 0.02$; $r = 0.94$, $p = 0.03$, respectively), and negatively correlated with the increase in renal arterial RI ($r = –0.91$, $p = 0.03$), renal and heart involvement ($r = –0.97$, $p = 0.03$ for both), total DU number ($r = –1$, $p = 0.02$), PAP values ($r = –0.94$, $p = 0.03$), and MES ($r = –0.83$, $p = 0.05$). No difference regarding the mean CN was noted between patients with ACA and anti–Scl-70 positivity.

Our present study reports for the first time, to our knowledge, on patients with SSc in the context of the "Late" NVC pattern of microangiopathy, an association between progressive decrease of absolute CN and organ involvement during a 5-year followup, despite different treatments.

It is known that the "Late" NVC pattern represents a bad prognostic factor and a marker of an SSc subset with worse prognosis[1,4,5], but it was not yet known what happens inside an SSc population with the constant "Late" pattern of microangiopathy.

The small sample size is one limitation of our study. This limitation was related to the inclusion criterion to enroll only SSc patients with "Late" NVC pattern of microangiopathy and with a recorded complete medical history and at least 5 years of followup. Further, this was an observational study to follow the progression of SSc damage in a selected cohort of patients, not considering possible effects of ongoing therapies.

Our investigation reports a progressive decrease of the absolute CN in advanced stages of the disease, which significantly correlates with progressive SSc organ involvement.

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Table 1. No. patients (%) with different SSc subset and organ involvement at different times during the followup.

	T0	T1	T2	T3	T4	T5	p*
lcSSc	21 (91)	21 (91)	18 (78)	17 (74)	15 (65)	15 (65)	0.0004
dcSSc	2 (9)	2 (9)	5 (22)	6 (26)	8 (35)	8 (35)	0.0004
New DU	9 (39)	5 (22)	8 (35)	8 (35)	8 (35)	11 (48)	ns
ED	17 (74)	19 (83)	20 (87)	21 (91)	21 (91)	21 (91)	0.014
ILD	11 (48)	15 (65)	18 (78)	18 (78)	22 (96)	22 (96)	< 0.0001
Kidney	2 (9)	2 (9)	4 (17)	4 (17)	5 (22)	5 (22)	0.019
PAH	0 (0)	0 (0)	0 (0)	1 (4)	2 (9)	2 (9)	ns
Heart	0 (0)	0 (0)	1 (4)	2 (9)	3 (13)	3 (13)	0.044

T0 = baseline, T1 = 1 year, T2 = 2 yrs, T3 = 3 yrs, T4 = 4 yrs, T5 = 5 yrs. p*: statistical significance (Friedman test). SSc: systemic sclerosis; lcSSc: limited cutaneous SSc; dcSSc: diffuse cutaneous SSc; DU: digital ulcers; ED: esophageal dysmotility; ILD: interstitial lung disease; PAH: pulmonary arterial hypertension (diagnosed by right-heart cardiac catheterization); ns: not statistically significant.

Table 2. Mean ± SD of clinical variables at different times during the 5-year followup and statistical analysis between single times.

	T0	T1	T2	T3	T4	T5	p*
CN	5.40 ± 0.99	4.95 ± 1.13	4.68 ± 1.17	4.40 ± 1.26	4.32 ± 1.24	4.23 ± 1.21	< 0.0001
MES	6.00 ± 1.21	6.30 ± 1.40	6.52 ± 1.12	6.74 ± 1.18	6.57 ± 1.31	6.65 ± 1.27	0.01
FVC	115.26 ± 25.01	112.00 ± 25.35	108.78 ± 26.86	104.91 ± 23.46	103.91 ± 23.20	103.04 ± 23.27	0.0001
DLCO/VA	83.26 ± 13.30	80.30 ± 14.79	74.96 ± 16.81	72.70 ± 17.80	70.48 ± 17.77	71.17 ± 14.21	< 0.0001
RI	0.66 ± 0.07	0.66 ± 0.06	0.68 ± 0.07	0.70 ± 0.07	0.70 ± 0.07	0.72 ± 0.07	< 0.0001
Total DU	0.70 ± 0.97	1.00 ± 1.45	1.48 ± 1.97	2.00 ± 2.61	2.61 ± 3.20	3.30 ± 3.71	< 0.0001
sPAP	32.00 ± 6.56	32.87 ± 6.31	33.61 ± 7.38	33.39 ± 7.99	34.78 ± 7.71	35.35 ± 7.51	0.1037
mRSS	11.55 ± 7.12	11.92 ± 7.15	12.5 ± 7.01	13.21 ± 7.24	14.57 ± 7.38	15.48 ± 7.57	0.0024

T0 = baseline, T1 = 1 year, T2 = 2 yrs, T3 = 3 yrs, T4 = 4 yrs, T5 = 5 yrs. p*: statistical significance (Friedman test). CN: nailfold capillary no./mm (distal row); MES: microangiopathy evolution score (range 0–9); FVC: forced vital capacity (% predicted, normal values > 80); DLCO/VA: DLCO per unit of lung volume (% predicted, normal values > 75); RI: renal arterial resistive index (normal values < 0.70); DU: digital ulcers; sPAP: echo-estimated systolic pulmonary arterial pressure (limit for cardiac catheterization > 40 mmHg); mRSS: modified Rodnan skin score; ns: not statistically significant.

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