Relationship between changes observed in nailfold capillaroscopy and serological profile, lung fibrosis, and elevated risk of pulmonary hypertension in patients with systemic sclerosis and mixed connective tissue disease

Karolina Niklas1, Arkadiusz Niklas2, Tatiana Mularek-Kubzdela1, Mariusz Puszczewicz1, Włodzimierz Samborski1

1Department of Rheumatology, Rehabilitation and Internal Diseases, Poznan University of Medical Sciences, Poznan, Poland
2Department of Hypertension, Angiology and Internal Medicine, Poznan University of Medical Sciences, Poznan, Poland
3Department of Cardiology, Poznan University of Medical Sciences, Poznan, Poland

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Abstract

Introduction: Microvascular changes play a significant role in systemic sclerosis (SSc) and mixed connective tissue disease (MCTD). The most serious complications of SSc and MCTD are lung fibrosis (LF) and pulmonary hypertension (PH).

Aim: To determine the relationship of the changes observed in capillaries with the serological profile, LF, PH, and finger ulcerations in patients with SSc and MCTD.

Material and methods: The tested group comprised 80 persons (61 SSc, 19 MCTD); mean age 53.6 ±13.6 years. Patients were qualified to the LF group based on HRCT. Likelihood of PH was determined using echocardiography. The presence of antinuclear antibodies (ANA) was assessed using indirect immunofluorescence, while ANA profile, and sclerosis profile were assessed using EUROIMMUN kits, and antiphospholipid antibodies (aPL) using the ELISA method. Capillaroscopy was performed using the Nikon CPS 160 optical microscope.

Results: The following were found: a relationship between occurrence of anti-SS-A (p = 0.006) and anti-centromere B antibodies (p = 0.012) and ramified vessels, between anti-SS-B and capillary haemorrhages (p = 0.019), a positive correlation between NOR90 antibodies and winding loops (p = 0.021), PM-Scl 100 antibodies and enlarged vessels (p = 0.033), a negative correlation between Scl-70 antibodies and winding loops (p = 0.033), and a relationship between aCL and winding loops (p = 0.002). No relationship between the capillaroscopy image and PH risk was found. A positive correlation was found between avascularisation areas and LF and between giant capillaries and finger ulcerations. A negative correlation was found between U1-RNP antibodies and finger ulcerations (p = 0.009), and a positive correlation between antibodies to fibrillarin and ulcerations (p = 0.028).

Conclusions: SS-A, SS-B and anti-centromere antibodies are associated with the late phase of sclerodermic microangiopathy. Avascularisation areas significantly correlate with a higher prevalence of LF. U1-RNP antibodies have a protective role, while anti-fibrillarin antibodies are the risk factor for finger ulcerations.

Key words: systemic sclerosis, mixed connective tissue disease, capillaroscopy, lung fibrosis, pulmonary hypertension.
it has been attempted to use the changes in NC as the predictor of visceral complications of CTD such as lung fibrosis (LF) and pulmonary hypertension (PH), which contribute to increased mortality among patients [7].

Another important aspect is the serological profile. Apart from SSC-specific antibodies (Scl-70) for generalized form (dSSc) and antinuclear antibodies for the limited form (ISSc) and MCTD (antibodies to U1 ribonucleoprotein (U1-RNP)), many other antibodies of clinical importance are detected in the serum of patients [8, 9].

**Material and methods**

The study was a retrospective analysis of medical histories of 121 patients with SSC and MCTD hospitalized at the Department of Rheumatology and Internal Diseases of the Poznan University of Medical Sciences in 2005–2017. In 87 patients with SSC, diagnosis was made or verified based on ACR/EULAR criteria of 2013 [10], and in 34 patients with MCTD, diagnosis was made on the basis of the criteria of Alarcón-Segovia and Villarel and/or Kasukawa [11, 12]. Clinical data were collected based on medical records: detailed medical history, data from physical examination, laboratory evidence (serology in particular), description of capillaroscopy examination, result of high-resolution computed tomography (HRCT) of lungs, echocardiographic findings, and right heart catheterization (RHC) results, if they were performed.

Ultimately, 80 patients (61 with SSC and 19 with MCTD) were qualified for the study, for whom NC findings were obtained. In all 80 patients, anti-nuclear antibody (ANA) titre was determined. Assessment of individual ANA antibodies, i.e. ANA-profile, and HRCT were performed for these patients. In 69 patients (59 with SSC and 10 with MCTD), the sclerosis profile was carried out to determine the presence of ANA antibodies, which are characteristic for SSC. A total of 42 patients (33 with SSC and nine with MCTD) were tested for the presence of antiphospholipid antibodies (aPL). The likelihood of PH in echocardiographic examination was assessed according to the ESC/ERS guidelines of 2015 [13]. Echocardiography reports of all patients were not detailed enough to meet the above criteria. Thus, finally the statistical assessment concerning PH risk included 60 patients (50 with SSC and 10 with MCTD). According to the above guidelines, patients were divided into three groups: low, moderate, and high probability for PH prevalence. Owing to the low number of members in the two last subgroups, they were combined for further calculations as a group of patients with elevated probability of PH prevalence (14 patients) vs. a group with low probability of PH prevalence (46 patients). Details on the methodology concerning echocardiography were described in our previous publication [14].

Capillaroscopy was performed using the Nikon CPS 160 optical microscope with an additional source of cool light. The examination was performed at 20–22°C after a patient adaptation period of 15–20 min. The capillaries of the nailfold in fingers II–V of both hands were examined. Prior to the test, a drop of immersion oil was applied on the skin of the examined area. For the purpose of the present test, the presence of the following were recorded in the patients: winding loops, enlarged vessels (four times larger than the normal vessels), giant capillaries (10 times larger than the normal vessels), ramified vessels (vessels possessing at least four branches), avascularisation areas (areas where at least three subsequent capillaries fell out in a row), and capillary haemorrhages.

The presence of ANA was assessed using the indirect immunofluorescent antibody technique. The presence of ANA at 1 : 160 dilution of serum (1 : 160 titre) or higher represented a positive result. The ANA profile and sclerosis profile were assessed by the immunoblot method using EUROIMMUN sets with automatic assessment (EUROLineScan software). In the ANA profile, the presence of antibodies to the following antigens was assessed: U1-RNP, Sm, SSA, Ro-52, SSB, Scl-70, PM-Scl, Jo-1, centromere B, PCNA, dsDNA, nucleosomes, histones, ribosomal protein P, and AMA-M2. In the sclerosis profile, the presence of antibodies to the following antigens was assessed: Scl-70, centromere A, centromere B, RNA 11 kDa, RNA 155 kDa, fibrillarin, NOR90, Th/To, PM-Scl100, PM-Scl75, Ku, PDGFR, Ro-52. The presence of aPL antibodies, including antiphospholipid antibodies (aCL) and antibodies to β2-glycoprotein-I (β2GPI), was determined using the ELISA method (polyvalent test detecting antibodies in IgG, IgM, and IgA classes).

HRCT was performed using a Siemens Emotions 16 slice device. Patients diagnosed with LF were patients, for whom presence of fibrogenesis or changes with “ground glass” or “honeycomb” nature was determined in the examination.

Echocardiography examinations were performed transthoracically using a GE Vivid 7 device with 3.5 MHz head at the 1st Department of Cardiology of the Poznan University of Medical Sciences.

**Statistical analysis**

Age was expressed as arithmetic mean and standard deviation.

The relationship between the presence of individual parameters in NC (presence of winding loops, giant capillaries, ramified loops, avascularisation areas, capillary
haemorrhages) and sex, smoking tobacco products, presence of ulcerations on finger pads, occurrence of individual antibodies (ANA profile, sclerosis profile, and aPL), and LF as well as elevated PH risk was calculated using the $\chi^2$ test. $P < 0.05$ was considered as statistically significant. CSS Statistica v.12.5 software package was used for the calculations.

**Results**

For the purpose of calculations, data of 80 patients with SSc ($n = 61$) and MCTD ($n = 19$) were analysed. Group characteristics are presented in Table 1.

Distribution of the individual antibodies in the examined group is presented in Table 2.

In the assessment of the relationship of individual NC parameters with the presence of individual antibodies in the ANA profile, a significant correlation of the presence of SS-A with the occurrence of ramified vessels ($p = 0.006$) and the presence of SS-B with the occurrence of capillary haemorrhages ($p = 0.019$) was found. In the sclerosis profile, the following were found: a positive correlation of antibodies to centromeres B with the occurrence of ramified capillaries ($p = 0.012$) (with relation to antibodies to centromeres A, this relationship is on the border of significance $p = 0.058$), presence of NOR 90 antibodies with the occurrence of winding loops ($p = 0.021$), and presence of PM-Scl 100 antibodies with the occurrence of enlarged vessels ($p = 0.033$). On the other hand, the presence of Scl-70 antibodies indicates a negative relationship with the occurrence of winding loops ($p = 0.033$). Among aPL, only the relationship between the presence of aCL and the occurrence of winding loops could be found ($p = 0.002$).

With regard to visceral complications, no relationship between the capillaroscopy image and elevated PH could be found. However, a positive correlation was found between the occurrence of avascularisation areas and lung fibrogenesis and between the occurrence of giant capillaries and finger ulcerative lesions. Details on the correlations are presented in Table 3.

Moreover, a negative correlation was found between the presence of U1-RNP antibodies and the occurrence of finger ulcerative lesions ($p = 0.009$), and a positive correlation was found between the presence of antibodies to fibrillarin and occurrence of ulcerations ($p = 0.028$).

**Discussion**

As a non-invasive and inexpensive examination, capillaroscopy has been widely applied in the diagnostics of microvascular injuries. Apart from the well-grounded diagnostic role in Raynaud’s phenomenon and CTD suspicion, it can also be used to monitor the course of the disease and assess the effects of therapy [1, 4, 15]. Moreover, an increasing importance has been given to its predictive value [16, 17].

NC is of particular importance in patients with SSc and diseases of the sclerosis spectrum (MCTD, PM, and DM). Owing to its characteristics, Cutolo et al. proposed a division of microangiopathy specific for SSc (so-called scleroderma pattern) into three periods: early, active, and late [18, 19]. According to this classification, the early image consists of singular giant capillaries and possibly a few capillary haemorrhages. The active phase is characterized by numerous giant capillaries and capillary haemorrhages, with reduced vessel density of 20–30% and presence of minor disorganization of the vessel architecture. The late phase is characterized by a significant reduction in vessel density, with the presence of avascular fields and vessel disorganization. Only singular giant capillaries, haemorrhages, and ramified capillaries can be observed.

**Table 1. Characteristics of the studied group**

| Parameter                          | Whole group $n = 80$ | SSc $n = 61$ | MCTD $n = 19$ | SSc vs. MCTD |
|------------------------------------|----------------------|--------------|--------------|--------------|
| Age [years]                        | 53.6 ±13.6           | 56.08 ±12.26 | 45.47 ±15.02 | $p = 0.003$  |
| Sex (F/M)                          | 72/8                 | 55/6         | 17/2         | $p = 0.978$  |
| dSSc/lSSc                          | 48/13                | –            | –            | –            |
| Duration of illness [years]        | 11.04 ±7.88          | 11.28 ±8.57  | 10.26 ±5.21  | $p = 0.627$  |
| Current smoking (yes/no)           | 11/69                | 10/51        | 1/18         | $p = 0.769$  |
| Positive family history of rheumatic diseases (yes/no) | 15/65                | 12/49        | 3/16         | $p = 0.878$  |
| Raynaud’s phenomenon (yes/no)      | 76/4                 | 58/3         | 18/1         | $p = 0.953$  |
| Digital ulcers (yes/no)            | 32/48                | 28/33        | 4/15         | $p = 0.347$  |
| LF (yes/no)                        | 34/46                | 32/29        | 2/17         | $p = 0.249$  |
| EP/LP of PHa                       | 14/46                | 13/37        | 1/9          | $p = 0.721$  |

*It affects only patients with complete echocardiographic data, so the number $n$ in individual subgroups is less than for other parameters. dSSc – diffuse systemic sclerosis, lSSc – limited systemic sclerosis, LF – lung fibrosis, PH – pulmonary hypertension, EP – elevated probability of PH, LP – low probability of PH.
In our study, we decided to refer only to individual changes observed in NC without their classification to specific phases.

Within the assessed correlation of changes in NC with antibodies in the ANA profile, we obtained a positive relationship between the presence of SS-A antibodies and ramified capillaries, and SS-B antibodies and haemorrhages. This relationship was observed for the first time in our study. Earlier studies only described the relationship between Scl-70 and the presence of active and late phase of sclerodermic microangiopathy [20, 21]. Corominas et al. examined 150 patients with Sjögren's syndrome, for whom capillaroscopy was performed. However, they did not find a relationship between SS-A and SS-B antibodies and changes characteristic for SSc [22]. Moreover, Capobianco et al. did not determine such a relationship in patients with Sjögren's syndrome [23]. Perhaps the SS-A and SS-B antibodies associated with

### Table 2. Distribution of the individual antibodies in ANA profile, sclerosis profile, and aPL

| ANA-profile | Whole group | SSc n = 61 | MCTD n = 19 | SSc vs. MCTD |
|-------------|-------------|------------|-------------|--------------|
| U1-RNP      | 23/57       | 4/57       | 19/0        | p < 0.00001  |
| Sm          | 5/75        | 3/58       | 2/17        | p = 0.812    |
| SSA         | 8/72        | 5/56       | 3/16        | p = 0.740    |
| Ro-52       | 22/58       | 11/50      | 11/8        | p = 0.054    |
| SS-B        | 3/77        | 3/58       | 0/19        | p = 0.412    |
| Scl-70      | 28/52       | 27/34      | 1/18        | p = 0.439    |
| PM-Scl      | 11/69       | 9/52       | 2/17        | p = 0.876    |
| Jo-1        | 0/80        | 0/61       | 0/19        | –            |
| Centromere B| 17/63       | 17/44      | 0/19        | p = 0.008    |
| PCNA        | 0/80        | 0/61       | 0/19        | –            |
| dsDNA       | 10/70       | 7/54       | 3/16        | p = 0.619    |
| Nucleosomes | 3/77        | 0/61       | 3/16        | p = 0.012    |
| Histones    | 2/78        | 0/61       | 2/17        | p = 0.054    |
| Ribosomal P protein | 1/79 | 0/61 | 1/18 | p = 0.237 |
| AMA-M2      | 5/75        | 4/57       | 1/18        | p = 0.962    |

| Sclerosis profile | Whole group | SSc n = 69 | MCTD n = 10 | SSc vs. MCTD |
|-------------------|-------------|------------|-------------|--------------|
| Scl-70            | 26/43       | 25/34      | 1/9         | p = 0.519    |
| Centromere A      | 14/55       | 13/46      | 1/9         | p = 0.777    |
| Centromere B      | 17/52       | 17/42      | 0/10        | p = 0.105    |
| RNA 11 kDa        | 1/68        | 1/58       | 0/10        | p = 1.000    |
| RNA 155 kDa       | 2/67        | 1/58       | 1/9         | p = 0.802    |
| Fibrillarin       | 7/62        | 5/54       | 2/8         | p = 0.669    |
| NOR90             | 1/68        | 0/59       | 1/9         | p = 0.145    |
| Th/To             | 4/65        | 3/56       | 1/9         | p = 0.861    |
| PM-Sc100          | 9/60        | 9/50       | 0/10        | p = 0.338    |
| PM-Sc75           | 12/57       | 12/47      | 0/10        | p = 1.000    |
| Ku                | 3/66        | 3/56       | 0/10        | p = 0.454    |
| PDGFR             | 2/67        | 2/57       | 0/10        | p = 1.000    |
| Ro-52             | 18/51       | 13/46      | 5/5         | p = 0.245    |

| aPL n = 42 | Whole group | SSc n = 33 | MCTD n = 9 | SSc vs. MCTD |
|------------|-------------|------------|-------------|--------------|
| aCL        | 3/39        | 3/30       | 0/9         | p = 0.586    |
| β2GPI      | 5/37        | 4/29       | 1/8         | p = 0.978    |
In the sclerosis profile, we observed a statistically significant positive correlation between the presence of antibodies to centromere protein B (CENP B) and ramified capillaries, and a similar correlation was also found for the presence of antibodies to centromere protein A (CENP A) and ramified capillaries on the border of statistical significance. However, Cutolo et al. found different conclusions, demonstrating that the presence of anti-centromere antibodies delays the formation of changes characteristic in the late phase of sclerodermic microangiopathy, including ramified capillaries [20]. Other authors have suggested that the presence of these antibodies is associated with changes in NC of a slow-pattern nature, which is linked to the presence of giant capillaries, a minor reduction in the number of vessels, and the absence of ramified capillaries [25, 26]. However, Herrick et al. demonstrated that the presence of anti-centromere antibodies, apart from finger ischemic changes, also correlates with visible changes in NC in the form of reduced vessel density, which is a characteristic of the late phase, similarly to ramified capillaries in the correlation described in the present study [27].

Moreover, we also obtained a correlation between the presence of antibodies to PM-Scl 100 and the presence of enlarged capillaries. These are primarily antibodies associated with the PM/SSc overlap syndrome, and their prevalence in SSc is estimated at 7.1% [28]. Hanke et al. described a correlation between these antibodies and a higher prevalence of digital ulcers [29]. We were unable to find earlier literature reports on antibodies to PM-Scl 100 in the aspect of changes in NC, and thus it should be assumed that the present observation is the first one of this type.

Another result obtained in the present study was the positive correlation between the presence of NOR 90 and aCL antibodies and the presence of winding loops in NC and a negative correlation between the presence of Scl-70 antibodies and winding loops. Interpretation of these correlations is difficult due to the fact that the definition of winding loops itself is not uniform [30]. It is one of the most frequent changes in NC, and it may occur in numerous other diseases outside of the sclerosis spectrum as well as in rheumatology (e.g., psoriasis, diabetes). Thus, the above correlations should be considered as results with a lower clinical importance.

In our study, we could not confirm the correlation of capillaroscopy picture with an elevated PH risk in patients with SSc and MCTD. However, the majority of authors associate PH prevalence with the late phase observed in NC, particularly with avascularisation areas [17, 31]. Riccieri et al. compared capillaroscopic examination in patients with SSc with both presence and absence of PH. In the obtained results, patients with PH exhibited the active and late phase image more frequently; the presence of avascularisation areas was particularly underlined [32]. Voilliot et al., based on their research, made a conclusion that capillaroscopy, along with echocardiography, is one of the factors enabling identification of patients with an elevated risk of developing PH [33]. Corrado et al. examined patients with both SSc and PH and patients with idiopathic PH in terms of microvascular diseases. Their results indicate that microangiopathy may occur in PH with any aetiology, not only in the course of CTD [34]. Hofstee et al. observed that reduced capillary density in NC not only correlates with the presence of PH, but also with its severity, in both, PH associated with SSc, as well as idiopathic [35]. In addition, Voilliot et al. observed a positive relationship between sclerodermic microangiopathy and cardiovascular complications other than PH [36].

In our study, we found a statistically significant positive correlation of avascularisation area prevalence in NC with the LF presence. This is not an isolated observation. Earlier reports described this correlation in patients with both SSc and MCTD [15, 37]. Marino Claverie et al. observed that apart from the presence of LF in HRCT, the late image of changes in NC was associated with deteriorated results of functional tests in patients with SSc [38]. Sánchez-Cano observed that reduced forced vital capacity (FVC) < 70% may be connected with the presence of the active phase in NC [39]. Corrado et al. compared patients with LF in the course of SSc, idiopathic LF, and chronic obstructive pulmonary disorder (COPD) in terms of changes in capillaroscopy. Microangiopathy in patients with idiopathic LF was less advanced than

### Table 3. Correlation between changes observed in NC and visceral complications

| Variable           | Winding loops | Enlarged capillaries | Giant capillaries | Loss of capillaries | Haemorrhages | Ramified/bushy capillaries |
|--------------------|---------------|----------------------|-------------------|--------------------|--------------|---------------------------|
| Elevated probability of PH | \( p = 0.727 \) | \( p = 0.232 \) | \( p = 0.691 \) | \( p = 0.173 \) | \( p = 0.137 \) | \( p = 0.684 \) |
| Lung fibrosis      | \( p = 0.658 \) | \( p = 0.502 \) | \( p = 0.142 \) | \( p = 0.019 \) | \( p = 0.751 \) | \( p = 0.763 \) |
| Digital ulcers     | \( p = 0.354 \) | \( p = 0.622 \) | \( p = 0.021 \) | \( p = 0.168 \) | \( p = 0.849 \) | \( p = 0.094 \) |

**PH** – pulmonary hypertension.
that in SSC. However, compared to patients with COPD, a significantly reduced density of vessels and traits of neoangiogenesis were found [40]. Thus, the conclusion drawn by the authors stating that microvascular injuries play a significant role in lung fibrogenesis, even in its idiopathic form, appears to be valid.

A digital ulcer is a serious SSC and MCTD complication. In our study, we observed a positive correlation between the presence of giant capillaries and ulcerative lesions. A similar observation was made by Lambova et al. who described the active phase in NC, which was primarily characterized by the presence of giant capillaries, as significantly associated with the presence of digital ulcers [41]. Apart from that, commonly occurring and long-lasting ulcerative lesions are associated with the presence of avascularisation areas and the late phase of sclerodermic microangiopathy [17, 31]. Silva et al. indicated the late pattern in NC as an independent predictor of finger ulcerative lesions, but they also mentioned the presence of endothelium dysfunction biomarkers (i.e. plasma endothelin-1 level) as the risk factor for ulcerative lesion prevalence [42]. Sebastiani et al. described the capillaroscopic skin ulcer risk index (CSURI). This index is defined by the formula $M \times D : N$. $M$ is the number of megacapillaries in 1 mm, $D$ is the dimension of the largest megacapillary and $N$ is the number of capillary loops in 1 mm. The result over 2.94 means a significantly higher risk of digital ulcers within 3 months after examination [43]. Moreover, we found a negative correlation between U1-RNP antibodies and the prevalence of ulcerated lesions and a positive correlation between the presence of antibodies to fibrillarin and digital ulcers. We could not find literature reports on the protective role of any antibodies to fibrillarin and digital ulcers. We could not find literature reports on the protective role of any antibodies to fibrillarin and digital ulcers. We could not find literature reports on the protective role of any antibodies to fibrillarin and digital ulcers. We could not find literature reports on the protective role of any antibodies to fibrillarin and digital ulcers.

The presence of SS-A, SS-B and antibodies to centro-meres in patients with SSC and MCTD is associated with significantly more frequent presence of changes characteristic of the late phase of sclerodermic angiopathy in the NC image. Antibodies to PM-Scl 100 correlate with the presence of enlarged capillaries.

The presence of avascularisation areas in the NC image. Antibodies to PM-Scl 100 correlate with the presence of enlarged capillaries. Antibodies to PM-Scl 100 correlate with the presence of enlarged capillaries. Antibodies to PM-Scl 100 correlate with the presence of enlarged capillaries. Antibodies to PM-Scl 100 correlate with the presence of enlarged capillaries.

U1-RNP antibodies have a protective role, while antibodies to fibrillarin are the risk factor for the occurrence of finger ulcerative lesions in patients with SSC and MCTD.

Conclusions
The presence of SS-A, SS-B and antibodies to centromeres in patients with SSC and MCTD is associated with significantly more frequent presence of changes characteristic of the late phase of sclerodermic angiopathy in the NC image. Antibodies to PM-Scl 100 correlate with the presence of enlarged capillaries.

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U1-RNP antibodies have a protective role, while antibodies to fibrillarin are the risk factor for the occurrence of finger ulcerative lesions in patients with SSC and MCTD.

Conflict of interest
The authors declare no conflict of interest.

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