

Capillaroscopic pattern in systemic lupus erythematosus and undifferentiated connective tissue disease: What we still have to learn?

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Abstract In rheumatology, specific is the capillaroscopic pattern in systemic sclerosis (SSc), the so-called “scleroderma type”. Capillaroscopic pattern in systemic lupus erythematosus (SLE) is less specific and includes a wide range of microvascular changes—“SLE-type” capillaroscopic pattern, non-specific findings and in a small percentage “scleroderma-like” pattern. The latter finding is currently associated with a potential subclinical overlap with SSc. Various microvascular changes have been observed in a different proportion of patients with undifferentiated connective tissue disease (UCTD). The aim of the study was to evaluate the capillaroscopic changes in SLE and UCTD. Patients from the following groups were included in the study: 30 female patients with SLE (mean age, 49 ± 15.4 years), 31 patients with UCTD (mean age, 50 ± 17 years; 30 females and 1 male); 34 age- and sex-matched healthy volunteers were examined as a control group. Nailfold capillaroscopy was performed using videocapillaroscope Videocap 3.0 (DS Medica). Capillaroscopic findings were compared with clinical and laboratory data of the patients. At capillaroscopic examination, the most frequent capillaroscopic changes in SLE patients were

the presence of elongated capillaries in 43 % (13/30), an increased tortuosity in 70 % (21/30) and a prominent subpapillary plexus in 60 % (18/30) of the cases. In 80 % (24/30) of the patients, dilated capillaries were found; in 6.6 % (2/30), giant capillary loops; and in 16.6 % (5/30), haemorrhages. In 50 % of the patients, an “SLE-type” capillaroscopic pattern was found. In 30 % (9/30) of the cases the capillaroscopic examination revealed “non-specific changes”, in 6.6 % (2/30) of the patients it was found a normal capillaroscopic pattern and in 13.3 % (4/30) a “scleroderma-like” pattern. Positive tests for ANA were detected in 73.3 % (11/15) of the patients with “SLE-type” capillaroscopic pattern. In all the patients with “scleroderma-like” capillaroscopic finding, positive autoantibodies with a high titre were found, without signs for overlap with other connective tissue disease (CTD). In two out of four patients with such capillaroscopic findings, a vasculitis of peripheral vessels was evident and in the other two secondary RP and high immunologic activity. A “scleroderma-like” pattern was found in 38 % (12/31) of the patients with UCTD. In 51 % (16/31) of the patients from this group, “non-specific” capillaroscopic findings were observed. For the evaluation of the predictive value of capillaroscopic pattern for the development of a distinct rheumatic disorder in patients with UCTD, a longer period of follow-up is necessary. In SLE patients, it has been found that capillaroscopic examination reveals microvascular changes also in the absence of RP. Here, the results from the study illustrate the correlation between capillaroscopic changes and immunological profile. “Scleroderma-like” capillaroscopic pattern may be observed in the context of active vasculitis of peripheral vessels as well as in patients with secondary RP and high immunologic activity. It does not have an obligatory association with an overlap syndrome with other CTD. Capillaroscopic findings in UCTD are heterogeneous.

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The potential of capillaroscopic examination in UCTD for evaluating the prognosis of the disease needs to be revealed through long-term follow-up.

Keywords Nailfold capillaroscopy · Systemic lupus erythematosus · Undifferentiated connective tissue disease

Introduction

Nailfold capillaroscopy is a non-invasive imaging technique for morphological analysis of nutritional capillaries in the nailfold area, which is of considerable importance for the evaluation of microcirculation in vivo. At present, the method is used mainly for the differentiation of primary Raynaud's phenomenon (RP) from secondary RP in rheumatic disease from the group of scleroderma-spectrum disorders. In rheumatology, specific is the capillaroscopic pattern in systemic sclerosis (SSc), the so-called "scleroderma type", which is characterized with the presence of giant capillaries, haemorrhages, avascular areas and neo-angiogenesis [1–11]. Analogous changes may be observed in other connective tissue disease (CTD) such as mixed connective tissue disease, overlap syndromes, dermatomyositis and polymyositis and are termed "scleroderma-like" capillaroscopic changes [2, 4, 7, 8, 12].

Capillaroscopic pattern in systemic lupus erythematosus (SLE) is less specific in comparison to SSc and the other above-mentioned diseases, in which "scleroderma-like" capillaroscopic pattern may be presented [2, 15]. The prevalence of RP in SLE is reported to be ranging from 10 to 45 % and it usually indicates a more benign course without tissue necrosis [13, 14]. Nailfold capillaroscopic changes in SLE include a wide range. According to some investigators, the majority capillaroscopic findings are non-specific [16]. The most frequently described specific changes in SLE are tortuous, meandering capillaries and bizarre formed loops [17], an increased length of capillaries [18, 19], an increased diameter [17] and a prominent subpapillary plexus [18, 19]. In a part of the studies, these changes specific for SLE have been termed "SLE-type" capillaroscopic pattern. Increased tortuosity can be found in 42 % of SLE patients, but in only 6 % of SSc patients [17, 18, 20]. The "scleroderma-like" capillaroscopic picture with dilated, giant capillaries, haemorrhages and avascular areas is a rare finding in SLE in contrast to other CTD. The frequency of the latter pattern is low, ranging from 2 to 9 % [9, 12, 19, 20], and slightly higher, as reported by Furtao—15 % [21]. A number of investigators have found a correlation between "scleroderma-like" capillaroscopic pattern and the presence of RP and anti-U1-RNP antibody. This finding is being explained with a potential subclinical overlap with SSc [8, 16, 21–23]. Data addressing the

association between abnormal capillaroscopic findings and positive anticardiolipin antibodies are contradictory. It has been found a lack of correlation [23], a negative correlation [21], and a positive association [24, 25]. The following mechanism could be proposed for the pathogenetic effect of antiphospholipid antibodies on microcirculation: direct damage of endothelial cells through upregulation of adhesion molecules, platelet activation, interaction with elements of the coagulation system and activation of the complement components. The relationship between microangiopathy and the presence of antiphospholipid antibodies could be explained by this cascade of pathologic changes [25, 26]. A correlation between the abnormal capillaroscopic pattern and other SLE-specific autoantibodies (anti-dsDNA and anti-Sm) [113] could be found, as well as with the disease activity evaluated by different disease indices (SLEDAI and ECLAM) [23, 25]. Besides, an association of abnormal capillaroscopic findings, especially a decreased capillary density and a reduced diffusion capacity, could be verified. It was speculated that the reduced number of capillaries in the nailfold area may be an indicator for pulmonary capillary loss [22, 27]. Nailfold capillaroscopy is thought to be useful for the evaluation of microcirculation in SLE patients especially in those with secondary RP.

The term "undifferentiated connective tissue disease" (UCTD) is used to describe a group of patients with features of systemic autoimmune disease, which lacks the characteristics of a well-defined rheumatic disorder. Some of these patients (1/4–1/3) develop a distinct rheumatic entity during the follow-up, the most frequent being SSc, SLE, rheumatoid arthritis and Sjögren's syndrome, but the majority of patients remain in a stable clinically and laboratory condition in the scope of the UCTD. Nagy et al. [12] found a "scleroderma-like" capillaroscopic pattern in 13.8 % of 65 patients with UCTD.

Aim of the study

The aim of the study was to evaluate the capillaroscopic changes in SLE and UCTD.

Patients and methods

Patients from the following groups were included in the study:

1. 30 female patients with SLE according to the current ACR classification criteria, 1982 [28]. The mean age of the SLE patients was 49 ± 15.4 years.
2. 31 patients with UCTD. This group of patients manifested with signs of CTD, but did not fulfil the

criteria for SSc, SLE or other definite CTD. The mean age of the patients from this group was 50 ± 17 years (30 females and 1 male).

34 age- and sex-matched healthy volunteers without history of vasospasm, rheumatic or other known diseases, who do not take any medications, were examined as a control group (mean age 49.76 ± 15.98 , 33 females and 1 male) ($p > 0.05$).

Nailfold capillaroscopy was performed using videocapillaroscope Videocap 3.0 (DS Medica) in the Department of Rheumatology and Clinical Immunology, Kerckhoff clinic, Bad Nauheim, Justus-Liebig University—Giessen, Germany. The following capillaroscopic parameters were evaluated: distribution, shape, width, length, mean capillary density, presence of avascular areas, haemorrhages, neoangiogenesis and visibility of subpapillary plexus. Nailfold capillaroscopy was performed using a high-end videocapillaroscope Videocap 3.0 (DS Medica, Italy). Measurements were taken with the software programme of the device, and all the measurements were taken in millimetre ($0.001 \text{ mm} = 1 \mu\text{m}$).

As dilated were classified capillaries with a diameter of the arterial limb wider than 0.015 mm ($=15 \mu\text{m}$) or a venous limb wider than $=0.020 \text{ mm}$ ($=20 \mu\text{m}$). As giant capillary loops were classified microvessels with diameter of either an arterial or a venous limb greater than 0.050 mm ($=50 \mu\text{m}$). As elongated were classified capillary loops with lengths longer than 0.300 mm ($=300 \mu\text{m}$). The haemorrhages are the extracapillary brown aggregations of erythrocytes. The mean capillary density was calculated as a number of capillary loops in the distal row per 1 mm . The avascular area was defined as a distance between two adjacent capillary loops from the distal rows greater than 0.5 mm ($=500 \mu\text{m}$) or above 0.3 mm ($300 \mu\text{m}$) in the proximal area [29]. Meandering capillaries, presence of more than one capillary loop in a single dermal papilla, ramified and bushy capillaries are the characteristic features of neoangiogenic capillaries and were classified, respectively.

All observations are made with the subjects in a constant temperature setting ($22\text{--}25 \text{ }^\circ\text{C}$).

For statistical analysis of the data, variational analysis, *t*-criterion of V. Goset (Student's *t* test and Fisher's exact test) and chi-square test were used. Results are shown as mean value/average \pm standard deviation (SD). The values of $p < 0.05$ were considered statistically significant. The study has been approved by the local ethical committee, and all patients signed an informed consent.

In the group of patients with SLE, the following immunologic tests were conducted by ELISA method: ANA immunofluorescence test, antibodies against extractable nuclear antigens (anti-dsDNA, anti-Ro, anti-La,

anti-Sm, and anti-RNP) and antiphospholipid antibodies (anticardiolipin IgG, anticardiolipin IgM, anti- β 2-glycoprotein IgG, and IgM classes).

Results

Capillaroscopic pattern in systemic lupus erythematosus

RP was found in 73 % (22/30) in the group of patients with SLE, and in 10 % (3/30) vasculitis of peripheral vessels was present. At capillaroscopic examination, the most frequent capillaroscopic changes in SLE patients were as follows: the presence of elongated capillaries in 43 % (13/30), an increased tortuosity in 70 % (21/30), and a prominent subpapillary plexus in 60 % (18/30) of the cases. In 80 % (24/30) of the patients, dilated capillaries were found; in 6.6 % (2/30), giant capillary loops; and in 16.6 % (5/30), haemorrhages. The mean capillary diameters of the arterial ($0.019 \pm 0.006 \text{ mm}$) and venous limb ($0.027 \pm 0.007 \text{ mm}$) in the examined group of patients were significantly wider than the values in age- and sex-matched healthy controls ($0.012 \pm 0.001 \text{ mm}$ for the arterial limb and $0.017 \pm 0.002 \text{ mm}$ for the venous limb, respectively) ($p < 0.05$). The mean capillary length in SLE patients ($0.245 \pm 0.111 \text{ mm}$) was found to be greater than that in healthy controls (0.199 ± 0.071), but the difference was not statistically significant ($p = 0.0505$). The mean capillary density in SLE patients (8 ± 1.46 capillaries/mm) was significantly lower than that in healthy subjects (10 ± 0.59 capillaries/mm) ($p < 0.05$).

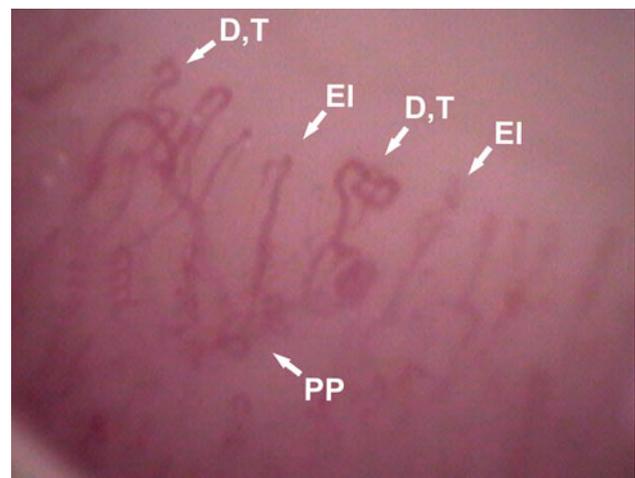


Fig. 1 “SLE-type” capillaroscopic pattern in SLE patient with secondary RP, demonstrating dilated and elongated capillaries, increased tortuosity, prominent subpapillary plexus, magnification 200x; *D* dilated capillaries, *EI* elongated capillaries, *T* tortuous capillaries, *PP* prominent subpapillary plexus

In 50 % of the patients, a “SLE-type” capillaroscopic pattern (with elongated capillaries, increased tortuosity, dilated capillaries and prominent subpapillary plexus) was found (Fig. 1). 73.3 % (11/15) of the patients with “SLE-type” capillaroscopic pattern were tested positive for ANA. In 54 % (6/11), the ANA titre was $\geq 1:640$. In 40 % (6/15) of the patients with “SLE-type” capillaroscopic pattern, positive tests for antibodies against extractable nuclear antigens were found, as follows: in 40 % (6/15) positive tests for anti-dsDNA, in 33 % (5/15) for anti-Ro antibodies, in 20 % (3/15) for anti-RNP antibodies. Anti-phospholipid antibodies (anticardiolipin antibodies IgG and IgM, and β -2 glycoprotein IgG and IgM classes) were negative in patients with a “SLE-type” capillaroscopic pattern.

In 30 % (9/30) of the cases, the capillaroscopic examination revealed “non-specific changes”, which included some of the above-mentioned changes (Fig. 2).

In 6.6 % (2/30) of the patients, it was found a normal capillaroscopic pattern and in 13.3 % (4/30) a “scleroderma-like” pattern. In all the patients with “scleroderma-like” capillaroscopic finding, positive autoantibodies with a high titre were found (Table 1), without signs for overlap with other CTD. In two out of four patients with such capillaroscopic findings, a vasculitis of peripheral vessels was evident (Fig. 3). In addition, “scleroderma-like” capillaroscopic changes were observed in two SLE patients with secondary RP and high immunologic activity (Fig. 4). The presence of a “scleroderma-like” capillaroscopic pattern is associated in the current literature with the presence of anti-RNP antibodies and overlap syndrome [16, 21–23]. In the examined group of SLE patients, such changes were observed in 4 patients, all of whom demonstrated high immunologic activity, but without signs for overlap with

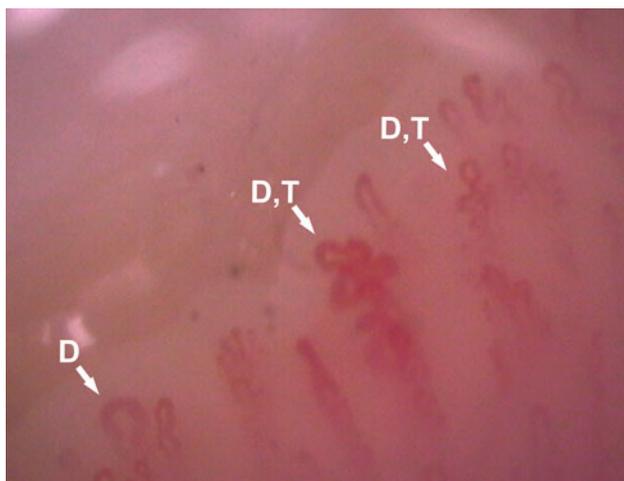


Fig. 2 Non-specific capillaroscopic changes in SLE patient without RP, demonstrating dilated (*D*) and tortuous capillaries (*T*), magnification $\times 200$

Table 1 Immunological profile in SLE patients with a “scleroderma-like” pattern

Antibodies	SLE cases			
	Case 1/with secondary vasculitis	Case 2/with secondary vasculitis	Case 3/without secondary vasculitis	Case 4/without secondary vasculitis
ANA	1:1280	1:10240	1:1280	1:10240
ENA (<20)	Negative	77.40	144	117
Anti-dsDNA (<100)	Negative	492	105.6	468
Anti-Ro (<20)	Negative	111	Negative	138
Anti-La (<20)	Negative	89.77	Negative	Negative
Anti-Sm (<20)	Negative	Negative	Negative	Negative
Anti-RNP-Sm	Negative	Negative	>200	Negative
Anticardiolipin IgG (<12)	Negative	Negative	28	Negative
Anticardiolipin IgM (<15)	Negative	Negative	52	Negative
Anti- β 2-glycoprotein (<20)	Negative	Negative	74	Negative
RF (<14)	102	Negative	Negative	Negative

other CTD. Active vasculitis of peripheral vessels was evident in two of them.

Capillaroscopic pattern in undifferentiated connective tissue disease

RP was found in 77 % (24/31) of the patients with UCTD. A “scleroderma-like” pattern was found in 38 % (12/31) of the patients with UCTD (Fig. 5). In 51 % (16/31) of the

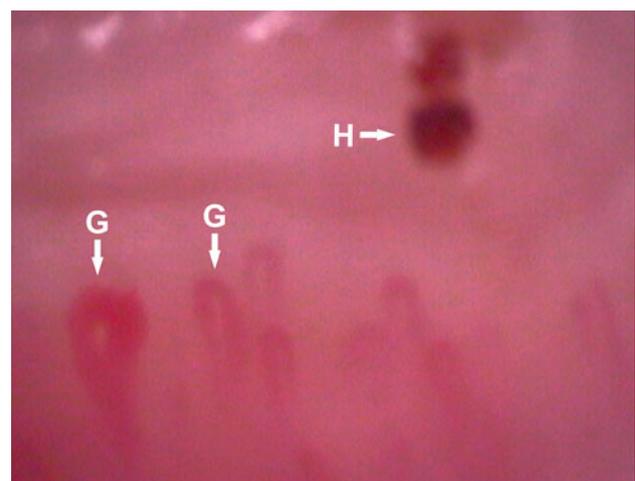


Fig. 3 “Scleroderma-like” capillaroscopic pattern in 40-year-old female patient with active vasculitis of peripheral vessels and high immunologic activity (case 2, presented in Table 1), magnification $\times 200$; *G* giant capillaries, *H* haemorrhage

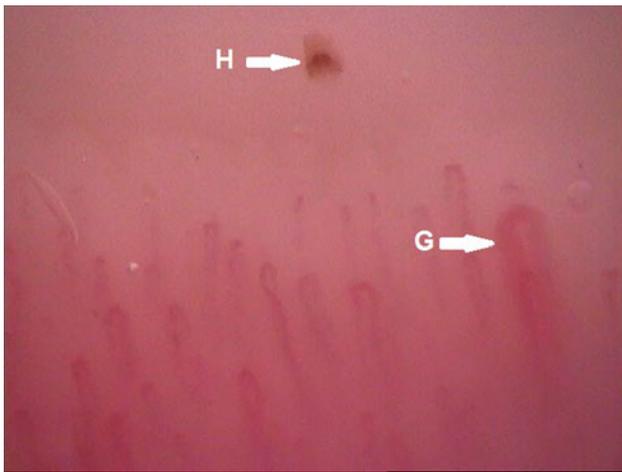


Fig. 4 “Scleroderma-like” capillaroscopic pattern in 78-year-old female patient with secondary RP, without peripheral vasculitis and high immunologic activity (case 4, presented in Table 1), magnification $\times 200$; *G* giant capillaries, *H* haemorrhage

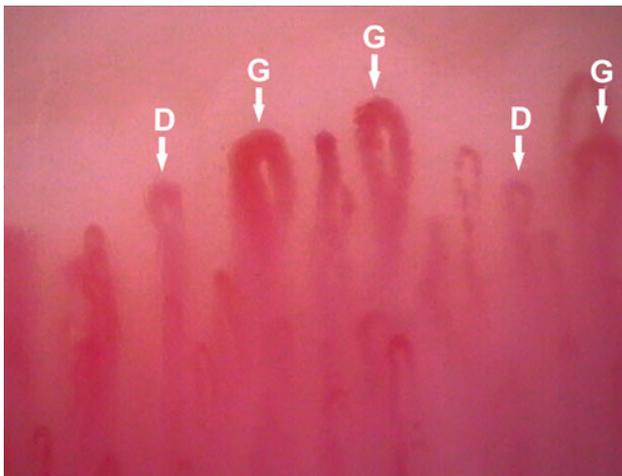


Fig. 5 “Scleroderma-like” capillaroscopic pattern in patient with UCTD and secondary RP, magnification $\times 200$; *D* dilated capillaries, *G* giant capillaries

patients from this group, “non-specific” capillaroscopic findings were observed, that is, dilated, elongated and tortuous capillaries either alone or in different combinations without any specific capillaroscopic pattern. In 9.6 % (3/31) of the patients, a normal capillaroscopic pattern was found. The mean diameters of the arterial (0.020 ± 0.007 mm) and venous limb (0.028 ± 0.012 mm) in patients with UCTD were significantly wider as compared with the respective values in healthy controls (0.013 ± 0.001 mm for the arterial limb and 0.018 ± 0.001 mm for the venous limb, respectively) ($p < 0.05$). The mean length of the capillary loop in UCTD patients (0.234 ± 0.090 mm) was found to be significantly longer as compared with those in healthy controls (0.197 ± 0.070 mm)

($p < 0.05$). The mean capillary density in patients with UCTD (8.2 ± 1.5 capillaries/mm; range, 5–12) was found to be significantly lower as compared with those in healthy subjects (10 ± 0.59 capillaries/mm) ($p < 0.05$).

A part of patients with UCTD (over 1/4–1/3) develop a distinct rheumatic disease during the follow-up, predominantly SSc, SLE or RA, but in the vast majority, the clinical and laboratory findings remain unchanged in the scope of the UCTD [12]. For the evaluation of the predictive value of capillaroscopic pattern for the development of a distinct rheumatic disorder in patients with UCTD, a longer period of follow-up is necessary.

Discussion

Capillaroscopic pattern in systemic lupus erythematosus

In the current study, the observed frequency of RP in SLE was 73 %, which is higher as those reported in SLE from most of the authors varying from 10 to 45 % [13, 14].

The results from the study demonstrate that capillaroscopic examination is useful for the evaluation of microcirculation in SLE, especially those with secondary RP, but microvascular changes may be also observed in the absence of RP. In addition, a correlation between the abnormal capillaroscopic changes, for example, “SLE-” and “scleroderma-like” type and the immunological activity of the disease, was found.

The presence of “scleroderma-like” capillaroscopic pattern is associated in the current literature with the presence of anti-RNP antibody and overlap syndrome [16, 21–23]. In the current study, such changes were found in four patients, all of whom demonstrated high immunologic activity, but without signs for overlap with other CTD. RNP was positive in all but one patient without signs for overlap. Active vasculitis of peripheral vessels was evident in two of them. Thus, it can be concluded that a “scleroderma-like” capillaroscopic pattern in SLE patients is not obligatory associated with overlap syndrome with other CTD. In the current study, it was observed in SLE patients with high immunologic activity presenting with peripheral ischemia in the context of active vasculitis of peripheral vessels or secondary RP without features of overlap syndrome with other CTD.

Capillaroscopic pattern in undifferentiated connective tissue disease

RP is a characteristic feature of UCTD. In the current study, RP was found in 77 % (24/31) of the patients from this group. A “scleroderma-like” pattern was observed in

38 % (12/31) of cases, “non-specific” capillaroscopic findings in 51 % (16/31) and normal capillaroscopic pattern in 9.6 % (3/31). Dynamic follow-up would reveal the predictive value of capillaroscopic pattern for the development of a distinct rheumatic disorder in patients with UCTD, particularly scleroderma-spectrum disorder or SLE in patients with more profound microvascular changes, observed at capillaroscopic examination.

Conclusions

In SLE patients, it has been found that capillaroscopic examination reveals microvascular changes also in the absence of RP. Here, the results from the study illustrate the correlation between capillaroscopic changes and immunological profile.

Although the presence of a “scleroderma-like” capillaroscopic pattern is associated in the current literature with the presence of anti-RNP antibody and overlap syndrome, such changes were found in 4 patients, all of whom demonstrated high immunologic activity, but without signs for overlap with other CTD. These changes were found in the context of active vasculitis of peripheral vessels as well as in patients with secondary RP and high immunologic activity. Thus, it could be concluded that the “scleroderma-like” capillaroscopic pattern in SLE patients does not have an obligatory association with an overlap syndrome with other CTD.

Capillaroscopic findings in UCTD are heterogeneous. The potential of capillaroscopic examination in UCTD for evaluating the prognosis of the disease needs to be revealed through long-term follow-up.

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