

CAPILLAROSCOPIC FINDINGS IN UNDIFFERENTIATED CONNECTIVE TISSUE DISEASE WITH RAYNAUD'S PHENOMENON

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Absrtact. Background: Undifferentiated connective tissue disease (UCTD) is characterized with presence of clinical signs and immunological findings suggestive of connective autoimmune disease, but the criteria for a definite rheumatic disease are not fulfilled. Raynaud's phenomenon (RP) could be found in approximately 50% of cases with UCTD and about half of patients with UCTD and RP exhibit "scleroderma-like" pattern. **The aim of the study:** To assess the characteristics of capillaroscopic changes in early UCTD. **Patients and methods:** Inclusion criterion for the study was newly diagnosed by rheumatologist, early UCTD in patients with RP. 26 patients were included in the study – 24 females and 2 males, mean age 38 ± 14 years (range 19- 66 years). Capillaroscopic examination was performed in all patients using USB microscope Dino-Lite. Follow-up was performed for a period between 1 and 3.5 years. **Results and discussion:** At the time of the initial diagnosis, "scleroderma-like" pattern, "early" phase (giant capillaries, presence of hemorrhages in some cases, preserved distribution, normal capillary density) was found in 17 patients (65%). More advanced capillaroscopic changes including devascularization and derangement were not observed. In 4 patients nonspecific capillaroscopic findings were present (dilated capillaries, hemorrhages, increased tortuosity, elongated capillaries,) and in 5 cases – normal capillaroscopic picture was found. During the follow-up in one patient the diagnosis was revised to systemic lupus erythematosus due to newly appeared clinical, laboratory and immunological findings. The normal capillaroscopic pattern was changed to nonspecific findings in this case. Two patients fulfilled the criteria for prescleroderma during the follow-up without skin and visceral involvement. In the rest patients clinical diagnosis and capillaroscopic findings remained unchanged. **Conclusion:** In conclusion, "scleroderma" type microangiopathy, "early" phase is a common finding in UCTD with RP, while more advanced microvascular pathology is not usually observed. Stable capillaroscopic pattern during the follow-up correlates with the stable clinical course. Capillaroscopy is a key technique for assessment of RP patients in rheumatology and for early diagnosis of UCTD with peripheral vascular syndrome.

Key words: undifferentiated connective tissue disease, capillaroscopy

INTRODUCTION

Undifferentiated connective tissue disease (UCTD) is characterized with presence of clinical signs and immunological findings suggestive of systemic autoimmune disease, but the criteria for a definite well-defined rheumatic disease are not fulfilled [1].

Classification criteria for UCDT approved by rheumatological scientific societies are lacking in contrast with other major connective tissue diseases. Thus, some patients with early phases of major rheumatic diseases could be classified as UCTD. There are observations that up to 30% of patients initially diagnosed with UCTD may evolve into a definite rheumatic disease few years after the initial diagnosis [2].

Mosca et al. (1999) have suggested classification criteria for UCTD that include:

- signs and symptoms of connective tissue disease, but the patients do not fulfill the criteria for well-defined rheumatic disease (systemic sclerosis (SSc), systemic lupus erythematosus, polymyositis/ dermatomyositis, primary Sjögren syndrome for a period of three years in association with
- positive antinuclear antibody/ANA test on two occasions.

If the duration of symptoms is below 3 years the condition is defined as early UCTD [1].

Currently, there are no accepted classification criteria and clinical practical guidelines approved by scientific rheumatological societies for diagnosis and management of patients with UCTD. Thus, patients with this diagnosis are neglected as compared with

other rheumatic diseases. Thus, individual experts' opinion guides risk assessment and the choice of appropriate therapeutic strategy [2]. Additional factor that contributes to poor understanding of UCTD is clinical heterogeneity i.e., existence of different clinical forms.

Rubio and Kyttaris (2023) performed a systematic review based on the analysis of 6 studies that included 1118 patients classified as UCTD. The most common reported symptoms were Raynaud's phenomenon (RP), sicca syndrome and arthralgias or arthritis [3].

De Angelis et al. (2005) in a study that included 78 patients with UCTD have found that RP is the second most common symptom with a frequency of 52.5% after the arthralgias that were observed in 80.7% of the examined patients. RP was with benign course without appearance of digital ulcers. Other clinical symptoms in the studied patient population were arthritis, sicca syndrome, photosensitivity. Visceral involvement was rare. Difference in the prevalence of articular involvement in patients with and without RP was not detected [4].

RP could be found in approximately 50% of cases with UCTD [4]. Considering the key role of capillaroscopy for assessment of RP, capillaroscopic microvascular assessment is of crucial importance in UCTD with symptoms of RP. Nailfold capillaroscopy is a non-invasive method for assessment of nailfold capillaries that has gained increased popularity in the recent years due to the key role for differential diagnosis in RP patients and early diagnosis of SSc. Currently, capillaroscopic changes in SSc are established as a diagnostic criterion in the 2013 EULAR (European League Against Rheumatism)/ACR (American College of Rheumatology) classification criteria for the disease [5]. The capillaroscopic changes in SSc are termed "scleroderma" pattern that is characterized with the presence of giant capillaries, hemorrhages, avascular areas and bushy capillaries i.e., neoangiogenic vessels [6, 7, 8]. Maricq et al. (1983) suggested staging of "scleroderma" type capillaroscopic pattern into two subtypes i.e., "slow" pattern characterized with presence of giant capillaries and minimal capillary loss and "active", in which there are extensive avascular areas and neoangiogenesis [8]. Cutolo et al. (2000) suggested validated staging system of "scleroderma" pattern in SSc that includes three phases of capillaroscopic changes i.e., "early", "active" and "late". "Early" phase is characterized with appearance of few giant capillaries and microhemorrhages, preserved capillary density and distribution. In the next "active" phase,

giant capillaries and microhemorrhages are frequent. In addition, moderate devascularization, mild to moderate capillary derangement could be found. Bushy capillaries are few or absent in this stage. In the next "late" phase devascularization and capillary derangement are advanced. Frequent ramified capillaries could be found, while hemorrhages are absent, giant capillaries are few or absent [9].

Analogous microvascular changes that are called "scleroderma-like" capillaroscopic picture could be found in diseases different from SSc such as dermatomyositis, overlap syndromes, UCTD as well as in systemic lupus erythematosus and rheumatoid arthritis without presence of overlap with SSc [7, 10-19]. Observation of microvascular changes similar to SSc was reported initially by Maricq et al. [20, 21]. About half of the patients with UCTD and RP exhibit "scleroderma-like" pattern [4, 15]. In an own study, in 31 patients with UCTD, the prevalence of RP was 77% (24/31). Scleroderma-like pattern was found in 38% (12/31) of cases. In a part of the patients, capillaroscopic examination revealed nonspecific changes [15].

Considering clinical heterogeneity of UCTD and lack of classification criteria of the scientific rheumatological societies, high prevalence of RP in UCTD and the key role of capillaroscopy for assessment of RP, we have aimed to perform capillaroscopic analysis in newly diagnosed cases with UCTD and RP.

AIM OF THE STUDY

To assess the characteristics of capillaroscopic changes in early UCTD.

PATIENTS AND METHODS

Inclusion criterion for the study was diagnosis early UCTD made for the first time by rheumatologist in patients with RP according to the criteria of Mosca et al. [1].

Exclusion criteria were presence of well-defined rheumatic disease i.e., SSc [22], systemic lupus erythematosus [23], mixed connective tissue disease [24], rheumatoid arthritis [25] the American Rheumatism Association, polymyositis/dermatomyositis [26, 27], primary Sjögren syndrome [28].

26 patients were included in the study – 24 females and 2 males, mean age 38 ± 14 years (range 19-66 years). Capillaroscopic examination was performed in all patients using USB microscope Dino-Lite, magnification x200. Follow-up was performed for a period between 1 and 3.5 years.

Definitions of the major capillaroscopic parameters suggested in the consensus of German-speak-

ing experts were used (Schmidt et al., 1997). Capillary diameter higher than 50 μm (0.050 millimeter/mm) is the known definition for giant capillary loop. Capillaries with arterial diameter $> 0.015\text{ mm}$ (15 μm) and venous $> 0.020\text{ mm}$ (20 μm), but below 0.050 mm (50 μm) are defined as dilated. Normal capillary density varies between 7 and 16 capillaries per mm. Devascularization is present when it is lower than 7 per mm. Capillaries with atypical morphology (bushy and branching microvessels) are considered neoangiogenic [29]. Presence of hemorrhages (extracapillary hemosiderin deposits) was assessed [30]. Capillaries with length longer than 300 μm were defined as elongated [31].

The “Fast Track algorithm” suggested by EULAR Study Group on Microcirculation in Rheumatic Diseases recommends quick differentiation between “scleroderma” and “non-scleroderma” pattern. In the presence of giant capillaries the changes are defined as “scleroderma” pattern. If capillary density is ≥ 7 capillaries/mm and giant capillaries are absent, capillaroscopic changes are classified as a “non-scleroderma pattern. If there is significant decrease in capillary density (≤ 3 capillaries/mm) in the presence of capillaries with atypical morphology, it is recommended to check for “late” scleroderma pattern [32]. Presence of giant capillary loops is a mandatory criterion for definition of the “scleroderma” pattern and it may be an isolated finding [33].

RESULTS

26 patients were included in the study during their initial referral to rheumatologist. The mean age of the patients was 38 ± 14 years (range 19-66 years); 24 females and 2 males.

All the patients exhibited symptoms of RP and the initial diagnosis was early UCTD according to the criteria suggested by Mosca et al. (1999) [1]. The mean duration of RP was 4.34 ± 4.41 years (range 3 months – 20 years). Presence of at least one non-Raynaud symptom was observed in all patients (24 patients – arthralgia, 8 – non-specific skin rash, 2 – chilblains/pernio, 2 patients – photosensitivity, 1 – arthritis, 1 – myalgia, 1 patient – digital ulcer of a toe). The mean duration of non-Raynaud symptoms was 1 year (range 1 month – 2 years).

At the time of the initial diagnosis “scleroderma-like” capillaroscopic pattern, “early” phase was found in 17 patients (65%) (Fig. 1, 2, 3). Presence of giant capillaries is a mandatory criterion for “scleroderma”/“scleroderma-like” capillaroscopic pattern i.e., the finding was present in all 17 cases with

“scleroderma-like” pattern. Preserved distribution and normal capillary density were also present in all 17 cases. Capillary density ≥ 7 capillaries/mm is an obligatory criterion for the “early” phase of “scleroderma”. Thus, the changes were classified as early “scleroderma” type microangiopathy. Hemorrhages were observed in 6 of these 17 cases. More advanced capillaroscopic changes with devascularization, derangement and neoangiogenesis were not found. In 4 patients nonspecific capillaroscopic findings were present (dilated/ $n = 4$, hemorrhages/ $n = 2$, increased tortuosity/ $n = 1$, elongated/ $n = 1$). In 5 cases, normal capillaroscopic picture was observed. In three patients with early microangiopathy and in one case with normal capillaroscopic picture, single neoangiogenic capillaries on a single finger were observed, but without accompanying devascularization and derangement that is not a definite sign of microangiopathy [34]. During 1-year follow-up in one patient the diagnosis was revised to systemic lupus erythematosus due to newly appeared clinical, laboratory and immunological findings. The normal capillaroscopic pattern in this case was changed to nonspecific findings. In two patients early, “scleroderma” type microangiopathy, the microvascular pathology was combined during the follow-up with SSc-associated autoantibodies i.e., anticentromere. These cases were labeled as prescleroderma according to the criteria of Le Roy and Medsger [35]. In these two patients, skin and visceral involvement was not detected for a follow-up over 3 years. In the rest patients clinical diagnosis and capillaroscopic findings remained unchanged for the period of follow-up (between 1 and 3.5 years).

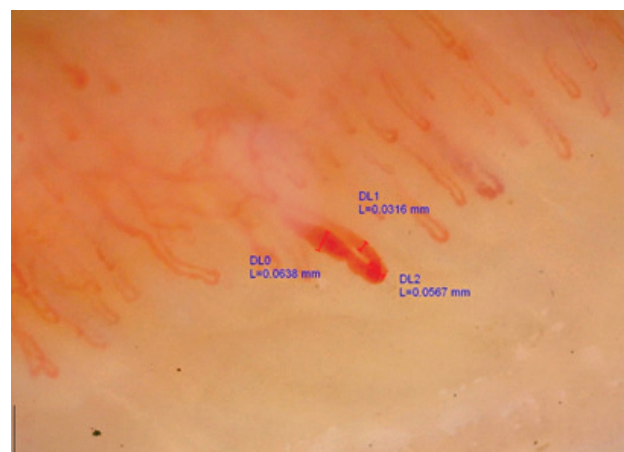


Fig. 1. Early phase, scleroderma-like pattern in 40-year-old woman. Capillary density and distribution are preserved. A single giant capillary loop is observed. Measurements of the capillary limbs of the giant capillary are demonstrated with venous limb = 0.0638 mm, apical loop = 0.0567

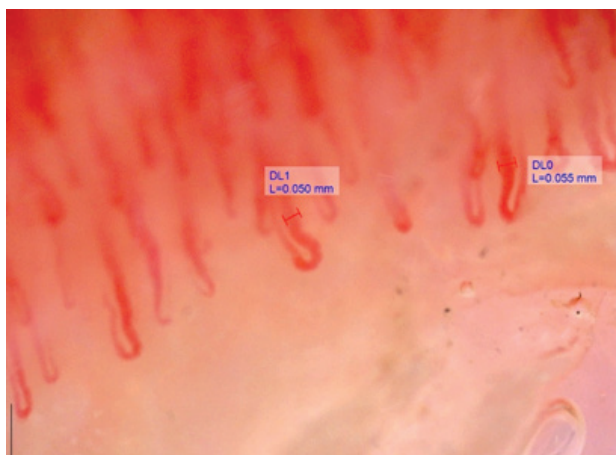


Fig. 2. Capillaroscopic pattern in 28-year-old male patient with UCTD. Distribution and capillary density are preserved. Presence of dilated and two giant capillaries is demonstrated. Measurement of the venous limbs of the giant capillaries is shown

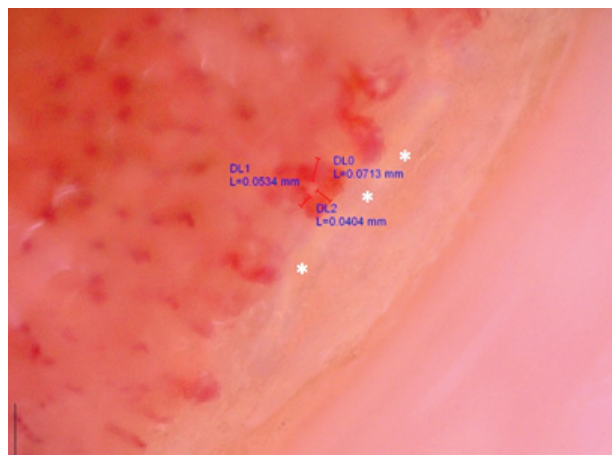


Fig. 3. Capillaroscopic pattern in 51-year-old female patient with UCTD. Distribution and capillary density are preserved. Presence of dilated and three giant capillaries (asterix) is demonstrated. Measurement of the diameters of centrally located giant capillary is shown

DISCUSSION

Capillaroscopic findings in UCTD with RP included presence of „scleroderma-like” capillaroscopic pattern, but also nonspecific findings and normal pattern. The most frequent non-Raynaud symptom in the studied patient population was arthralgia. These data confirm the observation of other author groups, who also report that arthralgia and RP are the most frequent clinical findings in UCTD [4].

The most frequent capillaroscopic finding in the studied patient population was “scleroderma-like” microangiopathy, “early” phase that was observed in 65% of cases. Similar are the results of the study of De Angelis et al. (2005) who have detected “slow” type “scleroderma” pattern (according to staging of Maricq) in 45% of patients with UCTD and RP (18/40). Dilated, giant capillaries and hemorrhages have been found, while devascularization and neo-angiogenesis was not detected. The follow-up was performed for a period of 12.8 ± 22 months. Significant dynamics in the parameters of the “scleroderma” pattern was not observed and only two patients developed well-defined rheumatic disease. The stability of the capillaroscopic changes in UCTD is associated with general characteristics of UCTD that is considered to be rheumatic disease with mild clinical presentation and minimal change during the follow-up [4]. In the current study the diagnosis UCTD also remained unchanged in the majority of the cases and worsening of early microangiopathy was not observed for a period over 3 years that correlates with the mild clinical course in these patients.

Our results differ from those reported by Merone et al. (2017) who have evaluated 42 UCTD patients with RP. Nonspecific capillaroscopic abnormalities were observed in most of the cases i.e., in 98% (40/42). Tortuosity and ramified/bushy capillaries were more frequent findings in UCTD patients. Presence of microhemorrhages and elongated capillaries were found more commonly in cases with evolution of UCTD to systemic lupus erythematosus ($n = 4$) for the period of follow-up (3 years) [36]. Different are also the observations of García-González et al. (2017) who have found normal capillaroscopic pattern in 56% of the studied UCTD patients (55/98). 37% of the cases ($n = 36$) exhibited nonspecific changes and only 7% (7) had „scleroderma” type pattern. The presence of altered capillaroscopic findings at baseline was more frequent in cases who have developed a definite connective tissue disease during the follow-up (64%) as compared with the stable UCTD (47%) and the patients who achieved remission (22%). RP was present in 89 patients (91%), 53 (54%) had musculoskeletal manifestation, 41 (42%) – cutaneous involvement, 27 (28%) – sicca syndrome, etc. The period of follow-up was 11 ± 3 years. 62% of the patients remained in the scope of the diagnosis UCTD, 24% achieved remission and 14% ($n = 14$) developed well-defined rheumatic disease i.e., 9 – systemic lupus erythematosus, 2 – prescleroderma, 1 – mixed connective tissue disease, 1 – SSc with diffuse cutaneous involvement and 1 – scleroderma-Sjögren overlap syndrome) [37]. The diverse results received by different au-

thors' groups underlines the necessity for further studies in larger patient populations.

CONCLUSION

The early microangiopathy in patients with UCTD and RP in the current study was observed in 65% of the cases. Considering non-specific clinical symptoms of UCTD and its mild, sometimes sub-clinical course, detection of capillaroscopic features of microangiopathy provides early diagnosis in this clinical entity. Thus, early referral of RP patients to specialized centers in rheumatology and mandatory capillaroscopic examination would give the opportunity for early detection, early therapeutic intervention that might prevent or retard disease progression.

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Постъпил за печат: 14.04.2023 г.

Submitted: 14.04.2023

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