Nailfold Capillaryoscopy – Its Role in Diagnosis and Differential Diagnosis of Microvascular Damage in Systemic Sclerosis

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Abstract: In the nailfold area, specific diagnostic microvascular abnormalities are easily recognized via capillaroscopic examination in systemic sclerosis (SSc). They are termed “scleroderma” type capillaroscopic pattern, which includes presence of dilated, giant capillaries, haemorrhages, avascular areas, and neoangiogenic capillaries and are observed in the majority of SSc patients (in more than 90%). LeRoy and Medsger (2001) proposed criteria for early diagnosis of SSc with inclusion of the abnormal capillaroscopic changes and suggested to prediagnose SSc prior to the development of other manifestations of the disease. It is a new era in the diagnosis of SSc. At present, an international multicenter project is performed. It aims validation of criteria for very early diagnosis of SSc (project VEDOSS (Very Early Diagnosis of Systemic Sclerosis) and is organized by European League Against Rheumatism (EULAR) Scleroderma Trials and Reasarch. Very recently the first results of the VEDOSS project were processed and new EULAR/ACR (American College of Rheumatology) classification criteria have been validated and published (2013), in which the characteristic capillaroscopic changes have been included.

Our observations confirm the high frequency of the specific capillaroscopic changes of the fingers in SSc, which have been found in 97.2% of the cases from the studied patient population. We have performed for the first time capillaroscopic examinations of the toes in SSc. Interestingly, “scleroderma type” capillaroscopic pattern was also found at the toes in a high proportion of patients - 66.7%, but it is significantly less frequent as compared with fingers (97.2%, p<0.05). In our opinion, the examination of the toes of SSc patients should be considered as it suggests an additional opportunity for evaluation of the microvascular changes in these patients although the observed changes are in a lower proportion of cases.

Thus, capillaroscopic examination is a cornerstone for the very early diagnosis of SSc. Patients with clinical symptoms of peripheral vasospasm (Raynaud’s phenomenon (RP)) in association with puffy fingers and/or sclerodactyly should be carefully examined. Hence, appearance of “scleroderma” type capillaroscopic changes in RP patients should be interpreted in the clinical context, because some of the components of this pattern may be observed in several other connective tissue diseases such as mixed connective tissue disease, undifferentiated connective tissue disease that are termed “scleroderma-like” capillaroscopic changes. Capillaroscopic examination is an obligatory screening method in these cases, but the pathologic capillaroscopic changes are not specific and their interpretation is in clinical context.

Keywords: Capillaroscopy, systemic sclerosis.

INTRODUCTION

Systemic sclerosis (SSc) is a connective tissue disease characterized by microvascular damage, fibrosis of skin and internal organs, and autoimmune disturbances. Specific diagnostic microvascular abnormalities are easily recognized via nailfold capillaroscopy. The nailfold capillaries become easily visible after placing a drop of immersion oil. They have been observed for the first time more than 30 years ago by Maricq et al. and are termed “scleroderma” type capillaroscopic pattern, which includes dilated, giant capillaries (diameter of either arterial or venous limb > 50μm=0.050mm), haemorrhages, avascular areas, and neoangiogenic capillaries [1-4].

The characteristic changes in SSc are observed in the vast majority of patients with overt SSc - 83-93% (Maricq) [2]. Bergman et al. (2003) found “scleroderma” type capillaroscopic picture in a smaller proportion of SSc patients - 70.4% [5]. Nagy et al. (2004) - in 87.5% of the SS patients with diffuse cutaneous involvement and in 61.6% of the cases with limited form of the disease [6]. In an own study, the specific “scleroderma” type capillaroscopic changes of the fingers in SSc patients were observed with frequency of 97.2% (35/36) [7]. The high frequency of the specific microvascular changes in SSc is thought to be the morphologic equivalent of the profound endothelial damage in the context of severe secondary Raynaud’s phenomenon (RP) in these patients, which also occurs in more than 90% of the patients [8]. Of note, some of the above mentioned capillaroscopic changes may be observed in other entities from the scleroderma-spectrum disorders, e. g. dermatomyositis, mixed connective tissue disease (MCTD), undiffer-
entiated connective tissue disease (UCTD) and are termed “scleroderma-like” capillaroscopic changes [1].

RAYNAUD’S PHENOMENON IN SYSTEMIC SCLEROSIS – LOCALIZATION AND SEVERITY

RP is the most frequent clinical symptom in SSC. It is a clinical manifestation of vasospasm of the peripheral arteries and arterioles as well as of permanent structural endothelial damage of the microcirculation. It presents in three or two phases, e.g. ischemia, asphyxia and reactive hyperemia with the respective skin colour phasic changes from pallor to cyanosis and redness. RP in SSC affects fingers, toes, nose, lips, earlobes. RP of the fingers is often the first clinical sign, that predates other symptoms of the disease by years. In a recent study of EUSTAR (EULAR (European League Against Rheumatism) Scleroderma Trial and Research), which included 7655 SSC patients, RP of the hands was found in 96.3% of the cases [9]. The most extensive study, addressing the frequency and type of foot involvement in SSC is those of La Montagna et al. in 100 SSC patients. RP at the feet has been observed with a similarly high frequency (90%) as at the hands (100%), but it has been noted to occur later in the disease course. Interestingly, RP of the feet presented at initial evaluation only in 43% of the patients, while in 47% it appeared in the course of the disease. In comparison, RP in the hands was found in 100% of the patients at the initial evaluation. In addition, skin score, necrotizing RP, tendon friction rubs were presented significantly less frequently in the feet of SSC patients as compared with the hands whereas arthralgias affected the feet significantly more often. Acrorheotaxis, calcinosis, and erosions were registered significantly more often in the hands of patients with SSC. These observations led to conclusion that foot involvement in SSC is less frequent, presents with later onset, but may cause similar disability [10]. In our own study, symptoms of RP of the feet were found in the vast majority of SSC patients (94.4%). Digital ulcers were observed with a lower frequency as compared with La Montagna et al. - 36% (13/36) of the patients in the fingers and in 8.3% (3/36) in the toes [7, 11].

CHARACTERISTIC FEATURES OF MICROVASCULAR CHANGES IN SYSTEMIC SCLEROSIS

The first capillaroscopic changes, which appear early in the course of SSC are a few number of dilated and/or giant capillaries and haemorrhages. Afterwards the number of giant capillaries and haemorrhages increases and in the late stages of the disease giant capillaries and haemorrhages are rarely observed and extensive avascular areas and inadequate neoangiogenesis appear. These distinct phasic changes are recognized and described by Cutolo et al. (2000):

i) an “early” phase is characterized by appearance of a few number of dilated and/or giant capillaries and haemorrhages. The distribution and capillary density are relatively preserved in this stage. These capillaroscopic changes are valuable for the early diagnosis of SSC.

ii) an “active” phase – the number of the giant capillaries and haemorrhages increases, there is moderate capillary loss, abnormalities in distribution. In addition, pericapillary oedema (light pericapillary halo) can be found.

A “late” phase is characterized by severe capillary loss, there are extensive avascular areas and the so-called desert-like areas may be found. Neoangiogenic capillaries appear in this stage, which are a morphological substrate of reparative, inadequate new blood vessel formation [4]. The neoangiogenic capillaries are bizarre-formed vessels, whose description include meandering, ramified, bushy microvessels, presence of more than one capillary loop in a single dermal papilla.

CAPILLAROSCOPIC CHANGES IN SYSTEMIC SCLEROSIS – THEIR ROLE FOR DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

It has been found that a number of patients with a definite diagnosis of SSC do not fulfill the ACR (American College of Rheumatology) classification criteria for the disease (1980) [12]. The diagnosis of SSC according to the ACR criteria (1980) is established on the basis of presence of one major criterion (skin thickening proximal of the metacarpophalangeal joints of the hands) or two minor criteria among the following, e.g. sclerodactyly, digital pitting scars, bibasilar pulmonary fibrosis [12]. Thus, patients with sclerodactyly, telangectasia, calcinosis, oesophageal involvement and other characteristic symptoms are not encompassed from these criteria. Of note, the abnormal “scleroderma” type capillaroscopic changes have been observed in these cases [6] The ACR classification criteria for SSC are highly specific. Thus, by using these criteria, an incorrect diagnosis is unlikely. It should be underlined, that they have been proposed prior to the discovery of SSC-specific capillaroscopic changes and SSC-specific autoantibodies. Hence, their sensitivity in early and very early SSC is low. It has been found that the inclusion of the specific capillaroscopic changes and the disease-specific autoantibodies, increases the sensitivity of ACR classification criteria for SSC [13, 14]. Based on this notion, LeRoy and Medsger (2001) proposed patients with objective signs of RP and abnormal nailfold capillaroscopic changes or positive SSC-specific autoantibodies (anticientromere, antitopoisoherase I, antifibrillarin, anti-PM-Scl, anti-fibrillin or anti-RNA polymerase I or III in a titer of 1:100 or higher) to be diagnosed as “prescleroderma” or limited SSC even in the absence of other disease signs. If RP is only subjectively reported by the patient, both “scleroderma” type nailfold capillaroscopic pattern and SSC-specific autoantibodies should be presented. The following options are accepted for objective documentation of RP:

1. Direct observation of any 2 among the known three phases of RP
   i) pallor (well demarcated whitening of acral skin)
   ii) cyanosis (dusky blueness, which disappears on rewarming)
   iii) well demarcated redness (reperfusion)
   or 2. Direct measurement of response to cold by
      i) objective evidence of delayed recovery after cold challenge
      ii) Nielsen test or equivalent [15].
The diagnosis of RP is clinical and is based on the direct observation of 2 among the 3 possible phases of the condition. To be given a diagnosis of RP, a patient must have a history of sensitivity to cold and episodic pallor, cyanosis or redness of the distal portions of the digits after exposure to low temperatures. Photographs of the hands can be obtained during an attack and used to confirm the history. In routine clinical practice it is not necessary to perform a cold provocation test to make a definitive diagnosis of RP [16]. According to the proposed criteria for early diagnosis of SSC of LeRoy and Medsger (2001), if RP is only subjectively reported by the patient direct measurement of response to cold should be performed. The recovery of the skin temperature of the hands after cold provocation test is below 15 minutes in healthy individuals and more than 20 minutes in RP patients. Nielsen test for the diagnosis of RP is introduced by Nielsen (1977) and represents a measurement of finger systolic blood pressure (FSBP) after cold provocation. Local cold provocation test may be performed (cooling the hands for 5 minutes at 15, 10 and 6°C) as well as combined local plus whole body cooling. FSBP is measured with an inflatable plastic cuff of the proximal phalanx of the thumb or at the middle phalanx of the fingers from 2nd to 5th. In healthy individuals, at standard temperature, the FSBP is identical to the blood pressure measured at brachial artery. The diurnal and between-day variations are between 5 and 10% in healthy people, which makes the method highly reproducible. The decrease of FSBP is a precise measure of cold-induced arterial vasoconstriction. In healthy individuals, the strongest decrease of FSBP after 5-minute cold provocation test during the next 15 minutes of evaluation is 60% from the initial values. An attack of RP is verified when FSBP is zero. The values of FSBP after cold provocation test between 60% of the starting values and zero (abnormal reaction) are found in patients with history of RP without induced vasospasm (false-negative results in milder forms of RP), in subjects with exaggerated subclinical cold reaction but without anamnestic RP and rarely as false-positive result [17].

At present, an international multicenter project is performed, that aims validation of criteria for very early diagnosis of SSC (project VEDOSS (Very Early Diagnosis of Systemic Sclerosis), organized by EUSTAR. The project is based on the notion, that the very early diagnosis of the disease provides the opportunity to delay the development of organ involvement via appropriate treatment. As red flags, which are indicators for referral of the patient to a VEDOSS center, are considered presence of RP, puffy fingers or sclerodactily, and positive antinuclear antibodies. In the VEDOSS centers, patients are screened via nailfold capillaroscopy and examination of SSC-specific autoantibodies. Those patients, who show abnormal capillaroscopic changes or positive SSC-specific autoantibodies, undergo further specific examinations. The primary goal of the project is registration of the proportion of patients, who will develop definite diagnosis SSC according to the ACR criteria (1980) during the follow-up or evolution of symptoms will be in a direction, which will lead to expert’s opinion for a definite diagnosis of SSC, but without fulfilling the ACR criteria [18, 19]. Patients with “prescleroderma” may evolve in definite SSC, in MCTD or in UCTD. The frequency of RP in the above mentioned connective tissue diseases is very high, as follows - 90-98% in SSC, over 80% in UCTD and 75-96% in MCTD.

During Phase 1 of VEDOSS project, potential items for revised SSC classification criteria were generated through two independent international consensus exercises performed by the Scleroderma Clinical Trials Consortium and the EUSTAR, resulting in a list of 168 potential items. A Delphi exercise of 105 international SSC experts reduced the list to 102 items. The item list was again rated and subjected to a consensus meeting using nominal group technique by a separate group of European and North American SSC experts, further reducing the list to 23 items. These candidate SSC items have proved to have good discriminant and construct validity in large cohorts of SSC patients and in comparison with non-SSc comparison patients, who have disease similar to SSC [20]. Finally, SSC classification criteria were reduced from 23 to 15 items by SSC experts as follows: skin thickening of the fingers proximal to the metacarpophalangeal joints, skin thickening of the fingers, finger tip lesions, finger flexion contractures, telangiectasia, abnormal nailfold capillaries, puffy fingers, calcinosis, RP, tendon/bursal friction rubs, pulmonary fibrosis, pulmonary hypertension, renal crisis, esophageal dilatation and SSC-related antibodies [21].

Very recently the first results of the VEDOSS project were processed and new EULAR/ACR classification criteria have been validated and published (2013), in which the characteristic capillaroscopic changes have been included together with several other newly established signs, e.g. SSC-specific autoantibodies, telangiectasias, RP, puffy fingers, pulmonary arterial hypertension (Table 1) [22, 23].

CAPILLAROSCOPIC CHANGES IN SYSTEMIC SCLEROSIS – OUR EXPERIENCE

In our own study, we have observed similarly to other authors [1, 2, 4] very high frequency of the specific nailfold capillaroscopic changes in the fingers of SSC patients - 97.2% [7, 24]. The first features of microangiopathy, which appear early in the disease course are dilated, giant capillary loops and haemorrhages. In healthy people, the capillaroscopic examination reveals hair-pin shaped capillary loops, parallel orientated with normal diameter, length and in every dermal papilla, there are one to three capillary loops (Fig. 1). It should be underlined, that the capillaroscopic picture of the same finger remains notoriously constant for long periods of time. We have found an association between the disease duration and the type of capillaroscopic alterations as proposed by Cutolo et al. (2000), who have described three distinct phases in SSC patients. In SSC patients in early stage of the disease (duration ≤ 3 years, n=10), in 50% of the cases an “early” phase, “scleroderma” type capillaroscopic pattern was observed. In the rest 50% (5/10) of the patients from this subgroup an “active“ phase, „scleroderma“ type capillaroscopic pattern was present (Fig. 2, 3). A “late” phase capillaroscopic changes were not observed in patients with short disease duration. In SSC patients with duration of the disease more than 3 years (n=26), a “late” phase capillaroscopic pattern was found in 26.9% (7/26) of the cases (Fig. 4), while the frequency of “early” phase capillaroscopic pattern in this group was only 7.7%, which is significantly less frequently as compared with patients with short disease duration.
Table 1. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League Against Rheumatism collaborative initiative [22, 23].

<table>
<thead>
<tr>
<th>Item</th>
<th>Sub-item(s)</th>
<th>Weight/Score</th>
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<tbody>
<tr>
<td>1. Skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints (sufficient criterion)</td>
<td></td>
<td>9</td>
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<tr>
<td>2. Skin thickening of the fingers (only count the higher score)</td>
<td>Puffy fingers; Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal inter-phalangeal joints)</td>
<td>2</td>
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<tr>
<td>3. Fingertip lesions (only count the higher score)</td>
<td>Digital tip ulcers; Fingertip pitting scars</td>
<td>2</td>
</tr>
<tr>
<td>4. Telangiectasia</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>5. Abnormal nailfold capillaries</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>6. Pulmonary arterial hypertension and/or interstitial lung disease (maximum score is 2)</td>
<td>Pulmonary arterial hypertension; Interstitial lung disease</td>
<td>2</td>
</tr>
<tr>
<td>7. Raynaud’s phenomenon</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>8. SSc-related autoantibodies (maximum score is 3)</td>
<td>Anticentromere; Anti–topoisomerase I (anti–Scl-70); Anti–RNA polymerase III</td>
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The total score is determined by adding the maximum weight (score) in each category. Patients with a total score of 9 are classified as having definite SSc.

Fig. (1). Normal capillaroscopic pattern of the finger of healthy individual. Hair-pin shaped, parallel orientated capillary loops with normal size (width and length) are demonstrated. The mean capillary density is preserved with a single capillary loop in every dermal papilla. (p<0.05). These results confirm that capillaroscopic changes in SSc differ during the course of the disease. Hence, the disease duration is not the only determinant factor for their development. The disease activity, the influence of angiogenic and angiostatic factors are potential contributing factors for the dynamic of capillaroscopic changes in different stages of SSc [7, 24].

Motivated by the high frequency of capillaroscopic changes of the fingers in SSc, we have performed for the first time capillaroscopic examinations of the toes in these patients (Lambova et al., 2011). In 84 healthy subjects, Noy Delcourt et al. (1986) observed that the majority of the toe capillaroscopic parameters are similar to those of the fingers, particularly the shape and capillary width. For other parameters the authors found some differences, such as a smaller number of capillary loops per mm, greater number of minor dystrophic forms, shorter capillary loops at the toes as compared with fingers. More frequent findings of the toes as compared with fingers were the irregularity in the distribution of the capillary loops and a peri-capillary haziness, which is associated with the physiological oedema of the feet [25]. Capillaroscopic pattern of the toe in a healthy individual is presented at Fig. (5). In our study, in 36 SSc patients the characteristic "scleroderma type" capillaroscopic pattern was found significantly less frequently at the toes — in 66.7% (24/36) vs. 97.2% (35/36) at the fingers (p<0.05), (Fig. 6), [7, 10]. All the key capillaroscopic parameters, which are markers for microangiopathy, e.g., giant capillaries, haemorrhages, avascular areas, and neoangiogenic capillaries were
Fig. (2). An “early” phase, “scleroderma type” capillaroscopic pattern of the finger of 52-year old female systemic sclerosis patient with 10 years duration of RP and 5 years duration of systemic sclerosis, a single giant capillary loop is demonstrated with a diameter of the venous limb 0.056mm (56µm).

Fig. (3). An “active” phase, “scleroderma type” capillaroscopic pattern of the finger of 67-year old female systemic sclerosis patient with 1 year duration of RP and systemic sclerosis.

Fig. (4). A “late” phase, “scleroderma type” capillaroscopic pattern of the finger of 67-year old female systemic sclerosis patient with 31 years duration of RP and SSc. Avascular area (arrow) and bushy capillaries (morphological substrate of neoangiogenesis) are demonstrated.

Fig. (5). A normal capillaroscopic pattern of the toe of healthy individual, which does not differ from the characteristic appearance of the normal pattern of the fingers.

Fig. (6). An “early” phase, “scleroderma type” capillaroscopic pattern of the toe of the same systemic sclerosis patient, presented at Fig. 2. A single giant capillary loop is demonstrated (arrow).

present, but with a significantly lower frequency at the toes as compared to the finger. Batticciotto et al. (2012) have also performed a study addressing the capillaroscopic microvascular changes at the toes of SSc patients and have concluded that feet examination is not useful for detecting the microvascular abnormalities in SSc patients. Batticciotto et al. did not observe haemorrhages of the toes in the examined group and found giant capillary loops only in a single case [26]. We have similarly found, that “scleroderma” type capillaroscopic changes are significantly less frequent at the toes as compared to the fingers, but our results differ significantly from those of Batticciotto et al., as we have detected the SSc-specific capillaroscopic findings also at the toes. We have observed lower frequency of the haemorrhages and giant capillaries of the toes vs those of fingers (8%, 3/36 vs. 58.3, 21/36, p<0.05 for haemorrhages and 30.6%, 11/36 vs. 77.7%, 28/36 for giant capillaries p<0.05). A possible explanation of these
findings is the absence of follow-up examinations. Considering the fact, that feet involvement in SSC frequently occurs later in the disease course, while RP of the hands is the most frequent presenting feature, which in a high proportion of patients precedes other phenomena of the disease by years, in our opinion microvascular changes of the toes may be observed later in the disease course. Thus, the examination of the toes of SSC patients should be considered as it offers an additional opportunity to evaluate the microvascular changes in these patients, although the observed changes are less prevalent.

Since 2001, when LeRoy and Medsger proposed new classification criteria for very early SSC with inclusion of the “sclerodermatous” type capillaroscopic changes, a new era for the role of capillaroscopy in the diagnosis of SSC began. Very recently new EULAR/ACR criteria for SSC (2013) have been validated and published with inclusion of the disease-specific capillaroscopic changes. This clearly demonstrates that the finding of the SSC-specific capillaroscopic features in patients with RP is diagnostic. Capillaroscopic examination facilitates prediagnosing of SSC before development of other features of the disease. Hence, the appearance of “sclerodermatous” type capillaroscopic pattern in RP patients should be interpreted in the clinical context, because some of the components of this pattern may also be observed in several other connective tissue diseases, e.g. dermatomyositis, MCTD, UCTD (“sclerodermatous-like” capillaroscopic changes) [1].

CONCLUSION

In conclusion, capillaroscopic examination is a cornerstone for very early diagnosis of SSC. A proportion of RP patients will develop a connective tissue disease during the follow-up. The detection of features of microangiopathy via, nailfold capillaroscopy is the best predictor for the underlying pathologic process. Patients with RP and puffy fingers and/or sclerodactyl should be carefully examined as prescleroderma, SSCs or UCTD may develop during the evolution of the symptoms. Capillaroscopic examination is an obligatory screening method in these patients and the capillaroscopic changes should be interpreted in clinical context.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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REFERENCES
