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REVIEW

The role of capillaroscopy in differentiation of primary and secondary Raynaud's phenomenon in rheumatic diseases: a review of the literature and two case reports

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Abstract The purpose of this study is to study and systematize the current knowledge about the role of capillaroscopy in differentiation of primary and secondary Raynaud's phenomenon (RP) in rheumatic diseases. This method is a review of the literature. Capillaroscopy is of crucial value for diagnosis and differentiation of primary and secondary RP in rheumatic diseases. The appearance of abnormal capillaroscopic pattern inherits high positive predictive value for the development of systemic rheumatic disease. The most specific pattern is found in systemic sclerosis (SSc), so called "scleroderma pattern", which is characterized by the presence of dilated capillaries, hemorrhages, avascular areas and neoangiogeneis. It is found in more than 90% of patients with overt SSc. Similar changes are found in patients with dermatomyositis, mixed connective tissue disease, undifferentiated connective tissue disease and they are called "scleroderma-like pattern". Absence of abnormal capillaroscopic findings can be regarded as a diagnostic criterion for primary RP. Inclusion of pathologic capillaroscopic pattern may increase the sensitivity of ACR classification criteria for SSc. In conclusion, capillaroscopy is of crucial importance for the differentiation of primary and secondary RP in rheumatic diseases, and also in differentiation between different forms of connective tissue diseases as well as for their early diagnosis.

Keywords Capillaroscopy · Raynaud's phenomenon · Rheumatic diseases

Introduction

Nail fold capillaroscopy is a non-invasive, inexpensive, easy to repeat imaging technique, which is of considerable importance for the evaluation of microcirculation in vivo [1, 2]. In rheumatology, the method is used in differentiation of primary and secondary Raynaud's phenomenon (RP) in rheumatic diseases. At present, capillaroscopy is still insufficiently applied in rheumatologic practice, rather by dermatologists or angiologists, thus prolonging the diagnostic process. In addition, the lack of guidelines for performing capillaroscopy, the ill-defined normal range of capillaroscopic parameters, and the imprecise interpretation of capillaroscopic patterns are the limiting factors for a widespread use in daily rheumatologic practice [3].

Results and discussion

Capillaroscopy is an imaging technique, which is used in medicine since 1823. In this year, Purkinje described skin capillaries when observing the nail-bed with a magnifying glass [4]. In 1911, Lombard found that after placing a drop of immersion oil capillaries become visible for examination by microscope, and 30 years ago, Maricq and Le Roy described the specific capillaroscopic pattern in systemic sclerosis (SSc) [1, 5].

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The cutaneous microcirculation

In most areas of the finger, capillaries in dermal papillas are located in a 90° angle to the skin surface so only the tip of the capillary loops can be seen with the form of a dot or a comma. These are nutritional capillaries, which represent 15% of the cutaneous microcirculation, and the rest 85% are used for thermoregulation. In the nailfold area, the capillary loops become more parallel to the skin surface, and in the last row they can be observed in their full length. The capillaries consist of an arterial and a venous part, and an apical loop, which connects these two. The arterial limb is narrower than the venous and the ratio of the venous-to-arterial diameter is approximately 1.2–1.5:1 [6].

Performing of a capillaroscopic examination

For visualization of capillaries a drop of cedar oil have to be placed. The patient is sitting with the hand at the heart level after a 15–20 min stay in a room with normal temperature of about 20–22°C [6–12]. The nailfolds of all 10 fingers should be examined. However, the most precise morphologic evaluation is obtained at the forth and fifth finger of both hands because of the highest transparency of the skin in these areas [8]. The following parameters are routinely evaluated: distribution, width, presence of dilated and giant capillaries, loss of capillaries, hemorrhages, tortuous, ramified and meandering capillaries, neoangiogenesis [5–7, 11–20]. A capillaroscopic finding is accepted as abnormal if changes are observed of at least two fingers [8].

Additionally videocapillaroscopy may evaluate functional status of skin microcirculation by measuring transcapillary diffusion of sodium fluorescein. Dynamic fluorescence videomicroscopy is an appropriate technique for detecting minimal microvascular changes. In healthy subjects, pericapillary diffusion of sodium fluorescein is characterized by the appearance of a thin pericapillary halo, while in SSc patients with secondary RP an irregular increase of capillary permeability can be found [2, 6, 8].

Equipment

At the beginning of the examination nailfold capillaries are examined with a light stereomicroscope that provides a magnification from 10× to 100×. For global evaluation of vessels in the entire nailfold area, wide-field capillaroscopy is used [6]. Other optical systems for visualization of capillaries (conventional optical microscopes, ophtalmoscopes, dermatoscopes) provide images with smaller magnification and lower quality, but they are useful, because are alternative choice to perform capillaroscopic examinations in cases that require bedside examination [7, 21, 22]. However, digital videocapillaroscopy, nowadays, is a gold standard and consist of the combination of a microscope and a digital videocamera. It provides a significantly higher magnification from 50× to 1000× and it allows capillaroscopic parameters to be measured precisely. Several capillaroscopic parameters: width, length and capillary density may be calculated by special software programmes [11, 12, 23, 24].

Indication for performing capillaroscopy in rheumatologic practice

The main indication for investigation in rheumatology are patients with RP, a common differentiated diagnostic problem in rheumatologic practice. RP is caused by a reversible vasospasm of the small arteries and arterioles of the fingers and toes provoked by cold temperatures. It manifests in three phases: ischemia, asphyxia and reactive hyperemia with skin discolouration from pallor to cyanosis and erythema. RP is classified into primary and secondary [1, 25]. Secondary RP is a common sequela in a number of rheumatic diseases and nailfold capillaroscopy plays a key role in differentiation of primary and secondary forms of RP [1, 3, 6, 8–12, 26, 27].

Capillaroscopic pattern in primary and secondary RP in rheumatic diseases

Primary RP

The diagnosis of primary RP can be made in these cases, in which no underlying causes for development of a vasospastic disorder can be identified. Women are 4–20 times more likely then men to develop primary RP. The onset of the disease is usually at puberty and is more frequent in certain families. Symmetrical vasospastic attacks and a benign course without trophic lesions is typical [25, 28–31]. Primary RP is often associated with migraine, retinopathy and Prinzmetal's angina. That suggests the hypothesis that RP is a systemic disorder with spasms not only of the peripheral arteries, but also with spasms of the coronary vessels, the arterioles of the lung, the brain, the retina and the gastrointestinal tract [31].

The absence of an abnormal capillaroscopic pattern is one of the diagnostic criteria for primary RP. For the diagnosis of primary RP the lack of the following criteria (Le Roy and Medsger) is required (a) digital ulcerations and gangrenes (b)elevated ESR; (c) positive test for antinuclear antibodies (ANA) with a high titer (d) abnormal capillaroscopic pattern [32]. Capillaroscopy in primary RP is not specific and the demonstrated capillaries are normal in number and size. The mean capillary diameter, capillary density and capillary morphology do not differ significantly from those of healthy subjects. The capillary diameter can be slightly enlarged, but it does not have a

diagnostic value [6]. In primary RP patients, Bukhari et al. [33] and Anderson et al. [23] found enlarged capillary loops in comparison with healthy subjects, which suggests minimal microvascular abnormalities. In a part of primary RP patients without signs and symptoms of a connective tissue disease (CTD) nailfold capillaroscopy may be abnormal and even dilated capillaries and avascular areas may be found [18, 34]. After a long duration of processes of ischemia and reperfusion permanent changes of microcirculation may develop. On the other hand, a part of primary RP patients with abnormal capillaroscopic changes will develop into a connective autoimmune disorder [18, 33]. Even the detection of a single loop with diameter >50 μm should be considered as a potential marker of microangiopathy and an indicator for future development of a CTD. It has been suggested that the appearance of dilated capillaries is due to a local response to tissue hypoxia [8, 11, 12]. Blockman et al. found enlarged capillaries in 100% of SSc patients, 56% of undifferentiated connective tissue disease (UCTD) patients, and 86% of dermatomyositis (DM) patients [8, 35]. RP may be an isolated complaint or a first symptom of CTD, so patients with manifestation of RP have to be regularly examined [29, 30, 36, 37]. Over a 10 year follow-up period the frequency of development of connective autoimmune disease is increasing from 5 to 19% [36, 37]. The capillaroscopic pattern of the same digit remains surprisingly constant for an extended period of time in healthy individuals, while appearance of abnormal findings inherits a positive predictive value of 47% for the development of a CTD. In combination with a positive ANA test and the presence of a rheumatoid factor, the predictive value increases up to 55% [38]. Therefore, nailfold capillaroscopy is of crucial importance for the differentiation of primary and secondary RP in rheumatic diseases. In presence of RP, a follow-up nailfold capillaroscopic analysis is recommended to be performed every 6 months [6, 11, 12, 28].

Secondary RP

Older age of onset, clinical features for autoimmune disease, trophic alterations of the fingers, positive autoantibodies and abnormal capillaroscopic findings are the characteristic features of secondary RP in rheumatic diseases [1, 29, 30, 39].

Systemic sclerosis

Raynaud's phenomenon is one of the most frequent symptoms in SSc with the frequency of approximately 90–95% and is usually the initial symptom that precedes other features of the disease by years. RP in SSc is severe and often presents with digital ulcers [29].

The capillaroscopic pattern in SSc is specific and is characterized by presence of dilated capillaries, loss of capillaries, avascular areas, hemorrhages and neoangiogeneis. It has been described for the first time by Maricq et al. [5] and is called "scleroderma type" capillaroscopic pattern [5, 6, 8–12, 18, 19, 22, 26]. Maricq et al. found that some of the parameters of this pattern can also be observed in mixed connective tissue disease (MCTD), UCTD, overlap syndromes, DM and define these findings as "scleroderma like" capillaroscopic pattern [6, 8, 11, 12, 19, 40]. However, the specific capillaroscopic pattern is found in a great number of cases with overt scleroderma—83–93% (Maricq) [5, 11]. Bergman and co-workers found this type of specific capillaroscopic changes in 70.4% of examined patients (19/27) [7], Nagy et al. in 87.5% of patients with diffuse SSc and in 61.6% of cases with limited form of the disease in 102 SSc patients [34]. Maricq et al. [18] describe two types of capillaroscopic changes in SSc, the "active" and "slow" pattern. In the patients with extensive, confluent avascular areas, neovascularization with a variable capillaroscopic pattern can be observed for short periods of time and reflects activity and progression of the disease (so called "active" capillaroscopic pattern). In contrast, the presence of giant capillary loops with minimal loss of capillaries is typical for the forms of the disease with a lower activity (so called "slow" capillaroscopic pattern) [6, 18, 41].

Cutolo et al. [9] described three phases of capillaroscopic changes in SSc:

(i) An early phase: appearance of few dilated and/or giant capillaries and few hemorrhages. In this phase, the distribution is relatively preserved without loss of capillaries. These findings are of crucial importance for the early diagnosis of SSc.
(ii) An active phase: there are high numbers of giant capillaries and hemorrhages. In addition a moderate loss of capillaries, slight derangement and diffuse pericapillary oedema can be found.
(iii) A late phase: it is characterized by severe loss of capillaries with extensive avascular areas, and ramified capillaries.

The capillaroscopic changes in SSc in the course of the disease is being explained by the action of different factors on angiogenesis. In the early stages of the disease, a pro-inflammatory state and an increased production of vascular endothelial growth factor stimulate angiogenesis. As a result, capillaroscopic analysis of the nailfold bed demonstrates the presence of microhemorrhages and tortuous, giant capillary loops, which are immature vessels formed during an angiogenic response. The short pro-angiogenic response is followed by a dramatic impairment of the angiogenic process. This switch is being explained by the

action of anti-angiogenic factors, which are thought to be markers for degradation of the extracellular matrix and other circulating proteins: angiostatin (a product of plasminogen cleavage), endostatin (of collagen XVIII), tumstatin (of collagen IV) and canstatin (of A2, IV collagen). Local tissue hypoxia and increased level of hypoxia induced factor also contribute to defective angiogenesis. As a result, in the following stages capillaroscopic examination reveals a reduced capillary density and extensive avascular areas [42]. Nailfold biopsy has confirmed the accuracy of capillaroscopic changes [41].

A relationship between capillaroscopic changes and the type of SSc, its activity and the visceral organ involvement has been claimed [6, 9, 10, 18, 26, 43–45], but not all authors do agree to this idea [17, 46]. Loss of capillaries, detected by nailfold capillaroscopy, are more common in patients with diffuse SSc, in whom the course of the disease is more severe, with rapidly progressive and fatal visceral organ involvement. In the limited form of SSc, RP and pulmonary hypertension are also more severe with later visceral involvement [45]. Cutolo et al. [10] found in 241 SSc patients, that presence of anti-topoisomerase antibodies (anti-Scl-70) correlates with "active" and "late" capillaroscopic changes and probably accelerate the appearance of these findings. Positive anticentromere antibodies (ACA) are more common in patients with an "early" capillaroscopic pattern and probably delay development of "late" capillaroscopic changes [10]. Bredemeier and co-authors [13] in 91 SSc patients ascertained a relationship between loss of capillaries at the nailfold beds, skin involvement and activity of pulmonary disease as evaluated by high-resolution computed tomography [13]. It has been suggested that the dynamics of the alterations of the capillaroscopic pattern at the follow-up of patients with CTD could be an indicator for visceral vascular involvement in the future [26, 40].

At present, for the diagnosis of SSc ARA/ACR criteria (1980) are used [47]. Nagy et al. found in 447 patients with CTD a high specificity of capillaroscopy for early diagnosis of SSc. Abnormal "scleroderma type" capillaroscopic pattern was found in patients who did not fulfill the ACR criteria and present with sclerodactyly, teleangiectasia, subcutaneous calcinosis, esophageal dysmotility and other symptoms. In 2001, Lonzetti et al. published a letter, in which authors evaluated the sensitivity of the ACR classification criteria for SSc in a group of 259 scleroderma patients. Using a regression tree analysis, they found that in limited Ssc, the inclusion of abnormal capillaroscopic pattern as criterion, the sensitivity of the ACR criteria could be improved from 33.6 to 82.9%. Adding of clinically visible capillary telangiectasias, increased sensitivity to 88.8%, and the presence of ACA increased the sensitivity further to 91.5% [37, 48, 49]. Hudson et al. [50] also confirmed that inclusion of the specific capillaroscopic changes as a criterion improves also sensitivity of ACR criteria for SSc [50]. ACR classification criteria for SSc are specific rather than sensitive and in using these criteria incorrect diagnosis is most unlikely. They have been proposed prior to the discovery of specific SSc capillaroscopic changes and autoantibodies. After 2000, three proposals for classification criteria of SSc have been published. The specific capillaroscopic pattern has been included in two of them—the criteria of Le Roy and Medsger [51] and the other presented by Maricq and Valter [52]. Le Roy and Medsger [51] and Nadashkevich et al. [53] proposed inclusion RP as a diagnostic criterion of SSc [37, 49, 51–53]. The high prevalence of microvascular abnormalities in SSc underscores the potential of RP and capillaroscopic changes for early diagnosis of the disease. To improve the early diagnosis of SSc, Le Roy and Medsger proposed patients with RP and abnormal nailfold capillaroscopic changes or positive specific for SSc autoantibodies to be diagnosed as "prescleroderma" or limited SSc even in the absence of other manifestation of the disease [6, 28, 38, 51].

Systemic lupus erythematosus (SLE)

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 [28, 38]. Capillaroscopy in SLE is less specific in comparison to SSc and the other above mentioned diseases in which "scleroderma-like" capillaroscopic pattern can be presented [6]. Nailfold capillaroscopic changes in SLE include a wide range. According to some investigators, the majority capillaroscopic findings are nonspecific [17]. The most frequent described specific changes in SLE are: tortuous, meandering capillaries and bizarre formed loops [20], an increased length of capillaries [15, 54], an increased diameter [20] and a prominent subpapillary plexus [15, 54]. In a part of the studies, these changes specific for SLE have been termed "SLE-type" capillaroscopic pattern [7, 20, 54]. The "scleroderma like" capillaroscopic picture with dilated, giant capillaries, hemorrhages 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% [7, 15, 18, 34] and slightly higher as reported by Furtado, 15% [57]. 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 [17, 55–57]. Data addressing the association between abnormal capillaroscopic findings and positive anticardiolipin antibodies are contradictory. It has been found a lack of correlation [57], a negative correlation [55], and a positive association [58, 59]. The following mechanism could be proposed for the pathogenetic

effect of anti-phospholipid antibodies on microcirculation—direct damage of endothelial cells through upregulation of adhesion molecules, platelet activation, interaction with elements of the coagulation system, activation of the complement components. The relationship between microangiopathy and the presence of anti-phospholipid antibodies could also be explained by this cascade of pathologic changes [58, 60]. A correlation between abnormal capillaroscopic pattern and other SLE specific autoantibodies, dsDNA, Sm [59] could be found, as well as with disease activity evaluated by SLEDAI [57, 59] and ECLAM indices [59]. 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 at the nailfold may even be an indicator for pulmonary capillary loss taken together [56, 61]. Nail fold capillaroscopy is useful for the evaluation of microcirculation in SLE patients especially those with secondary RP.

Dermatomyositis and polymyositis (PM)

The prevalence of RP in DM and PM is higher than 20% [28], but digital necrosis is not observed and if this is present, underlying malignancy should be suspected. The specific immunological marker of PM are anti-Jo-1 antibodies, which can be found in over 30% of the patients. Positive anti-Jo-1 antibodies in PM patients correlate with the presence of interstitial lung disease, RP and arthritis (anti-synthetase syndrome) [29]. The capillaroscopic pattern in DM is similar to that in SSc and has been defined by Maricq [19] as "scleroderma-like" pattern [19]. Bergman et al. found this "scleroderma-like" capillaroscopic pattern in 63.6% of 11 DM patients [1, 7], Nagy et al. in 26.9% of 26 DM/PM patients [34]. Enlarged capillaries are more common in DM patients than in those with PM. Avascular areas are found both in DM and in PM patients, but they are more frequent and more extensive in DM cases. The presence of a larger number of dilated capillary loops and more extensive avascular areas correlate with a higher frequency of RP and with pulmonary involvement in these patients [62]. In a recent study in 13 children with juvenile DM, Nascif et al. found a correlation between an abnormal capillaroscopic pattern, which in 12 of them is "scleroderma-like", and disease activity evaluated by manifestation of skin rash, a muscle weakness, elevated muscle enzymes and acute phase reactants [63].

Mixed connective tissue disease

The frequency of RP in MCTD is about 85% and often it is one of the initial symptoms [38]. MCTD patients with secondary RP often develop trophic abnormalities of the fingers. Anti-U1-RNP is a specific immune marker for the disease [29, 38, 64]. RP is included in the current classification criteria for MCTD (Allargon-Segovia and Villareal, Kasukawa et al., Sharp) [64]. The high incidence of RP in MCTD explains the essential role of capillaroscopic examination in these cases. Capillaroscopy is abnormal in the majority of patients. A "scleroderma-like" pattern with dilated capillary loops and avascular areas is present in 50–65% of patients [5, 7, 65]. The frequency of this specific capillaroscopic changes is lower in comparison to SSc patients. An association between the finding of avascular areas at the nail folds and lung involvement in MCTD could also be found [65].

Undifferentiated connective tissue disease

The term UCTD is used to describe a group of patients with features of systemic autoimmune disease that lacks the characteristics of a well defined rheumatic disorder. Some of these patients (1/4 to 1/3) develop a distinct rheumatic entity during follow-up, the most frequent: SSc, SLE,RA and Sjögren's syndrome (SS), but the majority of patients remain in a stable clinically and laboratory condition in the scope of the term UCTD. Nagy et al. found a "scleroderma-like" capillaroscopic pattern in 13.8% of 65 patients with UCTD. Thus, capillaroscopy should be performed in all cases with UCTD to identify those patients who are candidates to develop SSc or SLE [34].

Primary Sjögren's syndrome

RP is found in one-third of the patients with primary SS [28, 66]. It may precede the appearance of xerophthalmia and xerostomia or may manifest later in the course of the disease. Literature data demonstrate that RP in patients with primary SS are associated with milder course. In a part of the cases, the frequency of the vasospastic attacks and their severity may be reduced even without medical treatment [66]. However, capillaroscopy in SS is less specific. In patients with primary SS without manifestation of RP, Tektonidou et al. [67] found normal capillaroscopic finding in more than a half of the patients and "non-specific findings" in 42.8% including tortuous, crossed capillaries, capillary loops with irregular shape and a prominent subpapillary plexus. The mean capillary density in SS patients without RP did not differ significantly from those of healthy individuals. In SS patients, who present with secondary RP capillaroscopic changes were "non-specific" or classified as "other changes" including pericapillary and confluent hemorrhages. The frequency of normal capillaroscopic findings in this group of patients was about 12.5%, and in 12.5% of

patients "scleroderma-like" changes were found. The mean capillary density was significantly lower in comparison with the SS patients without manifestation of RP. In the subgroup of patients with primary SS and positive ACA, the investigators found 80% prevalence of a "scleroderma-like" capillaroscopic pattern, which suggests a potential subclinical overlap with limited SSc [67]. In primary SS patients, who present with secondary RP, Capobianco et al. [68] found also an abnormal capillaroscopy pattern being more frequent, and in a part of these cases they even observed a "scleroderma-like" capillaroscopic pattern. However, the authors could not confirm a correlation between abnormal capillaroscopic findings and positive ANA, SS-A or SS-B antibodies, nor with rheumatoid factor [68]. In 15 primary SS patients, Aguiar et al. [69] did not find significant differences between patients with and without secondary RP. These discrepancies may be explained with the different immunologic background of the examined patients [69]. These data suggest that capillaroscopy can be useful for the evaluation of microcirculation of SS patients, especially in those with secondary RP.

Rheumatoid arthritis (RA)

The prevalence of RP in RA is not well defined. Some authors consider that such an association is quite rare [29]. On the other hand, other authors include RA among the rheumatic diseases associated with RP [28, 32]. Grassi et al. [71] (Italy) found a low incidence of RP in RA—4.6% (19/411). The higher prevalence of RP in men with RA (7.5%) than in women (3.2%) was interesting. In comparison, a cohort of 919 patients with osteoarthritis, a global tendency of a female predominance of RP could be shown [70]. The higher prevalence of RP in men with RA has been explained by the authors with a higher association of RA with secondary vasculitis in men [29, 70]. These results are in agreement with the findings of Carrol et al. [70] (North Australia), who found a manifestation of RP in 2.7% of 141 patients with RA [71]. In a French population of RA patients, Saraux and co-workers found a higher prevalence of RP in RA—17.2%, (54/322) [72]. The contradictory literature data about the prevalence of RP in RA require future studies in different populations of RA patients.

In 31 RA patients, Redisch et al. found the following capillaroscopic changes: elongated capillary loops, increased tortuosity and a prominent subpapillary plexus [20]. A "scleroderma-like" pattern in patients with RA has not been found [16, 17, 34, 70, 73].

Abnormal capillaroscopic findings are described and in the absence of RP in different diseases such as primary antiphospholipid syndrome, psoriasis and psoriatic arthritis [74–76]. In addition, capillaroscopy can be potentially used for the monitoring of therapeutic response [6, 77–79].

Conclusions

Certain important conclusions for the daily clinical practice can be made as a result of the analysis of the literature:

1. Capillaroscopy is a non-invasive, easy to repeat imaging technique for the evaluation of microcirculation in vivo, which has also an favorable cost/effectiveness ratio.
2. The main indication for this technique in rheumatology are patients with RP, a common differentiated diagnostic problem in rheumatologic practice.
3. The method can be crucial for the differentiation of primary and secondary RP in rheumatic diseases, which are entities with different severity, prognosis and therapy. Thus, capillaroscopy should be performed in all patients with manifestations of RP, even when no clinical signs and laboratory tests indicating a distinct CTD are present, because appearance of abnormal capillaroscopic findings inherits a positive predictive value for the development of systemic rheumatic disease.
4. The most specific capillaroscopic pattern is the "scleroderma pattern". It is characterized by dilated capillaries, hemorrhages, avascular areas and neoangiogenesis and is found in about 90% of patients with clinically overt SSc [8, 11].
5. Similar changes in DM, MCTD, UCTD and overlap syndromes are called "scleroderma-like" capillaroscopic pattern.
6. The absence of abnormal capillaroscopic findings is one of the diagnostic criteria for primary RP. Inclusion of abnormal capillaroscopic pattern as a classification criterion in SSc patients markedly increases the sensitivity of the ACR criteria and facilitates early diagnosis.
7. Interestingly, a correlation between capillaroscopic finding, the clinical picture, laboratory tests and disease activity in rheumatic diseases could be found.

To illustrate the value of capillaroscopy in differentiation of RP in rheumatic diseases two case reports are presented.

Case report 1

We report a case of 58-year-old woman with a history of RP with an onset 9 months before the first visit at a rheumatologist. Careful clinical examination revealed only low skin temperature and oedema of the fingers without digital ulcerations. The results of complete blood cell count, acute phase reactants, urine analysis and the main biochemical parameters were within normal range. ANA was positive with a titer of 1:160, nucleolar fluorescence. Anti-Scl-70, anti-dsDNA, anti-Sm, anti-RNP antibodies and rheumatoid factor were negative. Serum immunoglobulins, C3 and C4

complement components were within normal range. In contrast, nailfold capillaroscopy revealed dilated and giant capillary loops, hemorrhages, preserved distribution, but no capillary loss. Chest radiograph was normal, diffusion capacity unaltered. No visceral involvement was found. The woman did not fulfil the ACR criteria for SSc, but she was diagnosed as prescleroderma, scleroderma incipiens or limited scleroderma according to classification criteria for early SSc as proposed by Le Roy and Medsger [51]. She started treatment with vasodilators—calcium channel blocker and inhibitor of phosphodiesterase—pentoxiphyllin. Three years later, at a follow-up, she presents with severe RP, digital ulceration and a substantial fatigue. At this visit, sclerodactyly, reduced diffusion capacity and bibasilar pulmonary fibrosis had developed. In summary, this case is a prototype how nailfold capillaroscopy indicate development of overt SSc and proves its crucial importance for an early diagnosis.

Case report 2

The second case is a 24-year-old woman with a history of RP. Three years after the onset of the vasospastic attacks, she developed symmetrical arthritis of wrists, metacarpophalangeal and proximal interphalangeal joints and morning stiffness, which lasted an hour. No muco-cutaneous or visceral involvement was found. Elevated acute phase reactants were found: ESR—30 mm/h, fibrinogen—5.2 g/l (<4.0 g/l), mild anemia with hemoglobin Hb—116 g/l; urine analysis—without proteinuria and normal sediment, transaminases—within normal range. Positive anti-CCP—15.80 IU/ml (<6.5 IU/ml), positive rheumatoid factor—118.43 U/ml (<25 U/ml), positive test for ANA with a titer of 1:160, diffuse fluorescence and negative anti-dsDNA could be found. X-ray of the hands was normal. In capillaroscopy, normal capillary density, form and distribution could be found. Significantly dilated or giant capillaries, avascular areas, hemorrhages and angiogenesis were also not found.

According to the EULAR recommendations for the management of early arthritis exclusion of other diseases than RA requires careful medical history, clinical examination, and at least the following laboratory tests: complete blood cell count, urine analysis, transaminases, and ANA test [80]. These investigations are necessary to differentiate RA from other rheumatic diseases such as CTD, reactive arthritis etc. because of the different prognosis and treatment. In SSc, overlap syndromes and MCTD, the majority of patients show a specific capillaroscopic pattern—the so-called “scleroderma” or “scleroderma-like” pattern, as outlined above. “Scleroderma-like” capillaroscopic changes are rare in SLE patients and was not found in RA patients. The absence of such changes in the presented case directs the diagnostic process to the following diseases: seropositive RA with positive ANA, overlap syndrome (RA, SLE) or SLE. Chloroquine therapy was started and the future course of the disease will reveal the underlying problem. These observations suggest that capillaroscopy inherits also a important diagnostic and prognostic value in patients with early arthritis and manifestation of RP.

In conclusion, nailfold capillaroscopy is useful in differentiating between primary and secondary RP, and also in differentiating between different forms of connective autoimmune diseases as well as for their early diagnosis.

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