Rheumatol Int (2012) 32:3039–3045
DOI 10.1007/s00296-011-2109-2

ORIGINAL ARTICLE

Scleroderma pattern of nailfold capillary changes as predictive value for the development of a connective tissue disease: a follow-up study of 3,029 patients with primary Raynaud's phenomenon

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Received: 29 March 2011 / Accepted: 22 August 2011 / Published online: 8 September 2011

Abstract To assess the prognostic value of scleroderma pattern of nailfold capillary changes for the development of connective tissue diseases (CTD) in subjects with primary Raynaud's phenomenon (RP). The study included 3,029 consecutive patients with primary RP who had been followed at 6-month intervals during the mean of 4.8 years. The pathological features of nailfold capillaroscopy were recorded in all patients who had neither clinical nor serological signs of a CTD. In patients who developed CTD, capillary changes obtained 6 months prior to diagnosis were analyzed. A possible relationship between capillary changes and the presence of associated CTD was assessed. At the end of follow-up, 1,660 (54,8%) patients have still the primary RP, 246 (8,1%) had suspected secondary RP, and 1,123 (37,1%) patients developed CTD (363 undifferentiated CTD, 263 systemic sclerosis, 143 systemic lupus erythematosus, 106 rheumatoid arthritis, 102 Sjögren's syndrome, 61 overlap syndrome, 30 vasculitides, 24 mixed CTD, 19 polymyositis, 7 dermatomyositis, and 5 primary antiphospholipid syndrome). Scleroderma pattern were significantly associated with the development of systemic sclerosis [$P = .00001$, sensitivity 94%, specificity 92%, positive predictive value 52%, negative predictive value 99%, and odds ratio 163 (95% CI, 97,9–271,5)], as well as dermatomyositis ($P = .0004$), overlap syndrome with signs of systemic sclerosis ($P = .0001$), and mixed connective tissue disease ($P = .007$). Capillary microscopy is effective method for differentiation between primary and secondary RP and useful tool for the prediction of scleroderma spectrum disorders in RP patients.

Keywords Capillaroscopy · Raynaud's phenomenon · Connective tissue disease · Systemic sclerosis

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Introduction

Raynaud's phenomenon (RP) represents a main sign of microvascular involvement in several autoimmune rheumatic diseases. RP is a vasospastic disorder characterized by episodic color changes in blanching, cyanosis, and hyperemia of the digits in response to cold or emotional stress. It can be classified as a primary phenomenon of unknown cause, or a secondary one related to a number of different diseases, including connective tissue diseases [1]. Most of the follow-up studies of subjects with RP noticed the development of associated connective tissue disease in 3–49% of sufferers [2, 3], but some investigators reported transition of up to 81% into connective tissue disease [4]. The mean time interval between beginning of RP and the development of connective tissue disease was 2–10.4 years [5, 6]. Early detection of connective tissue disease in subjects with RP is important and sometimes crucial for better treatment results and prognosis of the disease. Therefore, it is important to assess the prognostic significance of some diagnostic methods for the early detection of connective tissue disease in subjects with Raynaud's phenomenon. One of these methods is nailfold capillaroscopy. This simple noninvasive, inexpensive, easy to perform method is very important as a screening tool for detecting subjects with RP at high risk for the development of

connective tissue disease [2]. It has been proposed as a first-line investigation in the early differential diagnosis of Raynaud's phenomenon [7]. Significant changes in capillary morphology are present in 80% of adult with scleroderma and related disorders [8, 9]. That so-called scleroderma type (SD type) of capillary changes includes mainly decrease in capillary density, widened and giant loops often surrounded by avascular areas. The extent of microangiopathy detected by nailfold capillaroscopy has been shown to correlate with disease severity and prognosis [8, 10]. Furthermore, the presence of scleroderma type of capillary changes in adult patients with RP is thought to be indicative of the future development of connective tissue disease, even in the absence of other disease symptoms [2, 11]. However, long-term prospective studies of prognostic importance of nailfold capillaroscopy changes in large homogeneous groups of children and adolescents, as well as adult patients with long-standing primary and secondary RP, have not been conducted.

The aim of this study was to assess the prognostic value of SD type of nailfold capillary changes for the development of connective tissue disease in subjects with primary Raynaud's phenomenon.

Patients and methods

In the prospective outcome study, were enrolled 3,029 consecutive outpatients with diagnosis of primary RP according to the criteria proposed by LeRoy and Medsger [12]. Those subjects were recruited from our Nailfold Capillaroscopy Service. Study had been conducted during 10 years, from 1996 to 2006. At the first visit, all patients had symmetric attacks demonstrated as color changes in the hand and/or feet digits in response to cold or emotional stress, normal erythrocyte sedimentation rate, normal nailfold capillaries, negative test for antinuclear antibody, absence of tissue necrosis, ulceration, or gangrene, and absence of a secondary cause on the basis of a patient's history and general physical examination. Recruited patients had regularly follow-up visit every 6 months thereafter.

All the patients were subjected to a routine diagnostic procedure for the diagnosis of connective tissue disease. Initial evaluation of patients consisted of medical history, physical examination, and baseline blood tests. Serological tests included the assessment of antinuclear antibodies (ANA) by indirect immunofluorescence on the Hep-2 cell line substrate (Organtec Diagnostica, Germany). The other serologic and specific analyses were performed according to clinical features.

Informed consent was obtained from all participants prior to entry into the study. The study was approved by the local Ethic Committee.

Nailfold capillaroscopy was carried out using the semi-quantitative methodology described by Maricq [13], with some modifications by Damjanov et al. [14]. Briefly, an OPTON microscope with 16× and 100× magnifications was used. Cold light was provided by a Schott Mainy KL 150 fiber optic light source (50/60 Hz, 200 W, lamp 15 V/150 W, Germany). Patients were indoors for a minimum of 15–20 min before the examination, at a room temperature of 20–22°C. The nailfold capillaroscopy was carried out on eight fingers (excluding thumbs) on both hands of each patient, after a drop in immersion oil placed on the nailfold bed to improve resolution. Fingers affected by recent local trauma were not analyzed. Nailfold capillaroscopy was carried out by one experienced observer who was not aware of clinical and laboratory data at the time of examination.

Nailfold capillaroscopy changes in primary RP patients were not detected at the beginning of the study. After consecutive nailfold capillaroscopy in 6-month intervals, findings were classified as normal, nonspecific, or scleroderma like. Normal (typical hair pin structure or minor capillary morphological changes in distribution or size of loops), nonspecific (meandering and crossed capillaries, focal distribution of capillary hemorrhages, capillary thinning, capillary spasm, nonhomogenous distribution or size of loops, widening of the afferent, apical and efferent part of loop, linear elongation of the loop, shortened loops, prominent subpapillary plexus), and scleroderma type: "early", "active," or "late" capillaroscopy patterns as described by Cutolo et al. [7]. At the time of following controls in a number of patients, diagnosis of systemic connective tissue disease was evident using the established criteria [15–22].

For statistical comparisons, the χ^2 test with Yate's correction for continuity and Kruskal–Wallis test were performed. P values less than .05 were considered statistically significant. Sensitivity, specificity, positive and negative predictive values, and odds ratio were calculated as described previously [23].

Results

Patients summary

A total of 3,029 patients with primary Raynaud's phenomenon were included in the follow-up study of 4.8 years (range 1–10 years). The female/male ratio was 8:1, 2,696 (89%) patients were females and 333 (11%) males. The mean age at the onset of Raynaud's phenomenon was 38.1 years (range 6–68 years), and the mean age at the study entry was 43.4 years (range 8–79 years).

Follow-up data

Of 3,029 patients diagnosed as primary Raynaud's phenomenon, 1,660 (54.8%) had neither serological findings nor clinical signs of connective tissue disease during the

Table 1 Distribution of patients stratified according to diagnosis during the follow-up and the average duration of RP until the diagnosis

Diagnosis	Patients (*n*/%)	Duration of RP at diagnosis mean (range) years
Primary RP	1,660/54.8	N/A
Suspected secondary RP	246/8.1	N/A
Secondary RP		
UCTD	363/11.96	5.02 (0.5–54)
SSc	263/8.66	8.26 (0.5–54)
SLE	143/4.71	4.95 (0.5–30)
RA	106/3.49	4.14 (0.5–30)
Sjögren's syndrome	102/3.36	6.89 (0.5–63)
Overlap syndrome	61/2.01	7.08 (0.5–28)
Systemic vasculitides	30/0.99	4.68 (0.5–15)
MCTD	24/0.79	4.04 (0.5–18)
Polymyositis	19/0.63	3.19 (0.5–12)
Dermatomyositis	7/0.23	4.15 (0.5–20)
Primary antiphospholipid syndrome	5/0.16	6.4 (0.5–20)
Total	3,029/100	6.2 (0.5–54)

RP raynaud phenomenon, *UCTD* undifferentiated connective tissue disease, *SSc* systemic sclerosis, *SLE* systemic lupus erythematosus, *RA* rheumatoid arthritis, *MCTD* mixed connective tissue disease

follow-up period of 5.1 years (range 1–10 years). After 5.3 years (range 1–10 years) of follow-up period, 246 (8.1%) patients had no clinical signs of connective tissue disease but had serological findings or abnormal nailfold capillaroscopy, and they were considered to have suspected secondary Raynaud's phenomenon. After 4.3 years (range 1–10 years) of follow-up period, 1,123 (37.1%) patients developed connective tissue disease, and they were considered to have definitive secondary Raynaud's phenomenon. Among subjects with definitive secondary RP (patients with connective tissue disease), one-third ($n = 363$) had undifferentiated connective tissue disease (UCTD), one-fourth ($n = 263$) had systemic sclerosis (SSc), and around half of patients ($n = 626$) had other connective tissue diseases (Table 1). The mean time interval from the beginning of RP up to the diagnosis of a particular connective tissue disease was 6.2 years.

Distribution of different types of capillary findings in patients with primary, suspected secondary and definite secondary Raynaud's phenomenon

The distribution of different types of capillary findings in patients with primary, suspected secondary, and definite secondary RP is shown in Table 2. All patients with primary RP and most of the patients with rheumatoid arthritis (88%), UCTD (82%), Sjögren's syndrome (82%), systemic lupus erythematosus (75%), systemic vasculitides (70%), and polymyositis (68%) had normal capillaries. Half of the patients with mixed connective tissue disease (MCTD) had normal capillaries, and other half had nonspecific or SD type of capillary changes. The frequency of normal capillaries in the patients with primary Raynaud's phenomenon, rheumatoid arthritis (RA), and UCTD was significantly higher than in those with other connective tissue diseases ($P = .0013$). Nonspecific capillary changes were distributed equally in the patients with systemic lupus erythematosus (SLE), overlap syndrome, systemic vasculitis, and polymyositis. No patients with SSc or dermatomyositis showed normal capillary morphology.

Scleroderma pattern was present in 246 out of 263 (94%) patients with SSc, in 5 of 7 (71%) with dermatomyositis, in 28 out of 61 (46%) with overlap syndrome (all patients with SD pattern had signs of SSc), and in 9 out of 24 (37%) with MCTD. Only 11 (11%) patients with Sjögren's syndrome, 3 (10%) with systemic vasculitis, 14 (10%) with SEL, 32 (9%) with UCTD, 7 (7%) with RA, and 115 (6%) subjects with suspected secondary Raynaud's phenomenon had scleroderma-type nailfold capillary changes for at least 6 months before the expression of the disease. Scleroderma type of nailfold capillary changes significantly associated with the future development of SSc ($P = .00001$), and was significantly more frequent among patients with dermatomyositis ($P = .0004$), overlap syndrome with signs of SSc ($P = .0001$), and MCTD ($P = .007$) than among other patients.

Prognostic value of scleroderma type of nailfold capillary changes for the development of a connective tissue disease in patients with Raynaud's phenomenon

The sensitivity (Sn), specificity (Sp), positive and negative predictive value as well as odds ratio (OR), 95% confidence interval (CI) scleroderma type of nailfold capillary change for the diagnosis of connective tissue disease are presented in Table 3.

In patients with Raynaud's phenomenon developing SSc, the sensitivity (94%) and the specificity (92%) of SD type of nailfold capillary changes were higher than in the other connective tissue diseases. In all resumed connective tissue diseases, SD type of nailfold capillary changes had better negative than positive predictive value for the possible development of a connective tissue disease. Positive predictive value was generally low, except for the development of SSc (52%). The odds ratio for the development of SSc in patients who had SD type of capillary abnormality compared with those who had no abnormality was 163 (95% CI, 97.89–271.47). Also, in patients with Raynaud's phenomenon, SD type of nailfold capillary changes can predict the future development of dermatomyositis (OR 13.67), overlap syndrome with signs of SSc (OR 4.83), or MCTD (OR 3.30).

Table 2 Distribution type of nailfold capillaroscopic findings in patients with primary and secondary RP

Diagnosis	Nailfold capillaroscopic types (number of patients)			
	Normal	Nonspecific	Sclerodermic	Total
Primary RP	1,660	0	0	1,660
Suspected secondary RP	0	131	115	246
Definitive secondary RP				
UCTD	298	33	32	363
SSc	0	17	246	263
SLE	108	21	14	143
RA	93	6	7	106
Sjögren's syndrome	84	7	11	102
Overlap syndrome	22	11	28	61
Systemic vasculitides	21	6	3	30
MCTD	12	3	9	24
Polymyositis	13	6	0	19
Dermatomyositis	0	2	5	7
Primary antiphospholipid syndrome	2	3	0	5
Total	2,313	246	470	3,029

RP raynaud phenomenon, *UCTD* undifferentiated connective tissue disease, *SSc* systemic sclerosis, *SLE* systemic lupus erythematosus, *RA* rheumatoid arthritis, *MCTD* mixed connective tissue disease

Table 3 Sensitivity (Sn), specificity (Sp), positive (PPV) and negative (NPV) predictive value and odds ratio (OR), 95% confidence interval (CI) of scleroderma-type finding for the development of connective tissue diseases

Diagnosis	Sn (%)	Sp (%)	PPV (%)	NPV (%)	OR (95% CI)
UCTD	9	84	7	87	0.49 (0.34–0.71)
SSc	94	92	52	99	163 (97.89–271.47)
SEL	10	84	3	95	0.57 (0.33–1.01)
RA	7	84	2	96	0.37 (0.17–0.81)
Sjögren's syndrome	11	84	2	96	0.65 (0.34–1.22)
Overlap syndrome	46	85	6	99	4.83 (2.89–8.08)
Systemic vasculitides	10	84	1	99	0.60 (0.18–1.99)
Polymyositis	0	84	0	99	0
Dermatomyositis	71	84	1.1	99	13.67 (2.64–70,71)
MCTD	37	85	2	99	3.30 (1.43–7.59)

UCTD undifferentiated connective tissue disease, *SSc* systemic sclerosis, *SLE* systemic lupus erythematosus, *RA* rheumatoid arthritis, *MCTD* mixed connective tissue disease

Discussion

The results of our study are comparable with those of other authors, indicating that Raynaud's phenomenon principally affected females and in most cases, is not associated with the future development of connective tissue disease [6, 24, 25]. In our study, for both primary and secondary (suspected and definitive) RP, 89% of patients were female and approximately 55% of subjects with RP did not have recognized underlying connective tissue disease (primary RP). We showed that approximately 8% of subjects with RP during follow-up of 5.3 years had no clinical signs of connective tissue disease but had serological findings or abnormal nailfold capillaroscopy and they were considered to have suspected secondary Raynaud's phenomenon. We found that during the mean follow-up of 4.3 years, 37.2% of patients with RP developed connective tissue disease and were considered to have definitive secondary Raynaud's phenomenon. We have recorded spectrum of 11 different connective tissue diseases, most frequently the UCTD and systemic sclerosis. Harper et al. [26] found that connective tissue diseases have been developing during the follow-up, especially when capillary abnormalities are present at the first evaluation. Our results confirmed this tendency, because our patients who did not developed connective tissue disease (patients with primary RP) had normal capillaries during follow-up. The patients who developed connective tissue disease (patients with secondary RP) had

shown significantly more nonspecific capillary changes and SD type during follow-up. Our results showed that nailfold capillaroscopy helps distinguishing between primary and secondary Raynaud's phenomenon. We found a nonspecific or SD type of nailfold capillaroscopic finding in 41.6% patients with secondary RP; however, 24% of patients without any signs of a connective tissue disease after a mean follow-up of 5.3 years also showed pathological features in nailfold capillaroscopy suspected for connective tissue disease.

In our study, SD type of nailfold capillary changes were significantly associated with the future development of systemic sclerosis. In present study, approximately 94% patients with RP who developed SSc had SD type of nailfold capillary changes for at least 6 months before the expression of the disease. Also, patients who developed dermatomyositis, overlap syndrome with signs of SSc, MCTD had significantly more frequently SD type of capillary changes during follow-up than patients who developed other connective tissue diseases ($P = .0004$, $P = .0001$, $P = .007$, respectively). Among other connective tissue diseases, SD type was registered in 11% patients with Sjögren's syndrome, 10% with systemic vasculitis, 10% with SEL, 9% with UCTD, and 7% with rheumatoid arthritis. Also, we found SD type in 6% of subjects without any clinical signs and without or with laboratory signs of connective tissue disease after a mean follow-up period of 5.3 years. Similar to our results, Nagy and Czirják [27] noted SD type of nailfold capillaroscopic finding in 10% patients who had no clinical and laboratory signs of secondary Raynaud's phenomenon. The fact that both investigations had been performed in a tertiary reference center probably contributed to those high proportions. Maricq et al. [9] showed that capillary abnormalities occur not only in patients with SSc, but in related disorders, such as Raynaud's phenomenon, mixed connective tissue diseases, and dermatomyositis, but rarely in SLE patients.

The frequency of SD type in SLE patients is low, ranging from 2 to 9% [9, 27, 28], and slightly higher (15%) as reported by Furtado et al. [29]. In our study, only RP patients were included, which might be one reason for rather high incidence (10%) of SD type of capillary changes. On the other hand, in our SLE patients with SD type, 3 of them had anticentromere antibody (ACA) and 4 patients had anti-U1 ribonucleoprotein (anti-U1-RNP) antibodies (data is no shown). The presence of ACA in SLE patients was described in many reports [30–32]. Nakano et al. [30] suggested that RP patients with ACA may represent a distinct SLE subgroup. Sarkozi et al. [33] found that nailfold capillary microscopy findings may suggested a transition to limited SSc (variant of CREST syndrome: calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia) in SLE patients associated with ACA. Furtado et al. [29] found correlation between SD type and the presence of RP and anti-U1-RNP antibodies in SLE patients. Also, we consider that RP patients who developed SLE and had SD type and ACA/anti-U1-RNP antibodies could be part of a new SLE subset with subclinical features of systemic sclerosis.

Data addressing the association between abnormal capillaroscopic findings and positive anticardiolipin antibodies are contradictory. It has been found a lack of correlation [34], a negative correlation [29], and a positive association [35]. The following mechanism could be proposed: the direct damage of the endothelium by these antibodies [36]. In our SLE patients, only one had anticardiolipin antibodies and nonspecific capillaroscopic changes. Among 5 patients who developed primary antiphospholipid syndrome during follow-up, 2 of them had normal and 3 had nonspecific capillaroscopic pattern.

Our study showed a higher rate of normal capillaroscopic pattern in most patients with connective tissue diseases. One cause is difference in methods used for classification of normal and nonspecific findings. However, there is still no accepted method for the classification of the examined capillary parameters for prognostic purposes. Jouanny et al. [37] classified nailfold capillary patterns into 4 classes: normal, nonspecific finding (minor abnormalities), other findings (major abnormalities), and scleroderma pattern. Fitzgerald et al. [38] and Luggen et al. [39] defined normal and abnormal capillary patterns on the basis of distribution and morphology of capillary loops without areas of avascularity or capillary loop dropout. Regardless of difference in classification of normal and nonspecific pattern, we did not find specific capillary changes predictive for the future development of RA, UCTD, SLE, Sjögren's syndrome, vasculitis, psoriatic arthritis, and ankylosing spondylitis in subjects with Raynaud's phenomenon.

Similar to our results, Tektonidou et al. [40] showed that in patients with Sjögren's syndrome, normal and nonspecific findings were predominant. Only 2 of 16 patients (12.5%) had scleroderma type, and they were ACA-positive. Authors have proposed that patients with RP, Sjögren's syndrome, scleroderma pattern in capillaroscopy, and ACA should be included in the spectrum of limited SSc (lSSc), although no cutaneous scleroderma was observed. The time of lSSc diagnosis varies among individuals, and it is possible that some patients may present an atypical form of the disease for many years. In our 102 Sjögren's syndrome patients, RP was predominant among symptoms. Also, sicca symptoms and generally clinical and serological features of Sjögren's syndrome were present after 6.9 ± 9.16 years from the beginning of Raynaud's phenomenon. According to clinical features, we requested ACA in only 21/102 patients. More than half of them (11/21) had ACA, and 8 of these ACA-positive patients had

scleroderma pattern (data is no shown). Our conclusion is similar to other authors that patients with RP who developed Sjögren's syndrome and who had ACA and SD type should be a potential subclinical overlap with limited systemic sclerosis.

The data indicate that in RA patients there is usually not reported SD type [41]. In our study, we describe 5 RA patients with SD type of capillaroscopic changes. Three of them had ACA, and one had antitopoisomerase I (Scl-70) antibodies (data is not shown). Zimmermann et al. [42] described three ACA-positive RA patients with RP who developed lSSc 11, 29, or 50 years, respectively, after the onset of RA. In these patients, he did not perform analysis for the type of capillaroscopic changes. In our study, the mean duration of RP until developing RA was 4.1 years. Thus, it is likely that additional lSSc features would have become apparent with additional long-term observations.

The data showed that some of patients with UCTD (1/4 to 1/3) develop a particular connective tissue disease during follow-up, the most frequently SSc, SLE, RA, and Sjögren's syndrome [43], but the majority of patients remain in a stable clinical and laboratory condition during this period. Nagy and Czirják [27] found that 8 out of 65 cases with UCTD (13.8%) showed SD capillary pattern. Only three of eight patients had Raynaud's phenomenon. In our study, all patients had RP and 32/363 (9%) had SD type, as well as permanently stable clinical laboratory condition during follow-up.

The relative risk defined as odds ratio has been shown in two studies. Zufferey et al. [5] reported that an abnormal nailfold capillary pattern (OR 26.82) and an abnormal pulmonary function test result (OR 4.78) were strongly associated with the future development of connective tissue diseases. Ohtsuka et al. [43] found that the abnormalities of nailfold capillaries (OR 21.8) and swell hand (OR 18.5) were independent predictors of the development of SSc in patients who are diagnosed as having an early UCTD. Our results also confirm that SD type of nailfold capillary abnormalities can be the best predictor of the development of SSc (OR 163), or dermatomyositis (OR 13.6), overlap syndrome with signs of SSc (OR 4.83), and MCTD (OR 3.30). Also, we showed that SD type of nailfold capillary abnormalities had both diagnostic and prognostic significance for the eventual development of SSc in patients who are initially having primary RP [(higher sensitivity (94%) and specificity (92%), better negative (99%) than positive predictive value (only 52%)].

In conclusion, follow-up of 3,035 pts with Raynaud's phenomenon showed high rate (37.2%) of the future development of connective tissue diseases. Scleroderma type of capillary changes, found at least 6 months before the development of connective tissue disease, strongly suggested future development of systemic sclerosis, dermatomyositis, overlap syndrome with signs of systemic sclerosis, or mixed connective tissue disease. Capillary microscopy seems to be a useful tool for early selection of those patients who are potential candidates for developing scleroderma spectrum disorders. Nailfold capillary microscopy may not be a valuable diagnostic tool in SLE, RA, Sjögren's syndrome, but it might be helpful in identifying a subgroup of patients with different evolution and prognosis of the disease. Normal capillary pattern or nonspecific capillary changes were predominant findings in patients with primary Raynaud's phenomenon, as well as in those who developed UCTD, Sjogren's syndrome, SLE, RA, systemic vasculitides, and primary antiphospholipid syndrome. In the presence of Raynaud's phenomenon, a follow-up nailfold capillaroscopic analysis is recommended to be performed every 6 months.

Acknowledgments We are indebted to Ministry of science of Republic of Serbia. This study was supported by research grant number 17541 for 2011–2014, issued by the Ministry of science of Republic of Serbia. We thank Prof Dr Pavle Milenkovic for helpful comments on the manuscript.

Conflict of interest The authors declare that they have no conflict of interest.

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