Usefulness of vailfold capillary microscopy in the diagnosis of Raynaud's phenomenon

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Abstract

Nailfold capillary microscopy (NCM) is an easy and non-invasive test that enables observation of the capillaries.

Raynaud's Phenomenon (RP) can be the manifestation of an underlying systemic illness, therefore it would be useful to have an easy test that makes it simpler to distinguish the primary from the secondary type.

The aims of this study were: to evaluate which capillary microscopic changes are more frequent in RP; to analyze the informative value of the different criteria; and to determine the validity of NCM for the diagnosis of RP.

The clinical files of patients observed by NCM due to RP were evaluated. They were classified into three groups, according to the capillaroscopic criteria: primary RP, secondary RP due to a probable Connective Tissue Disease (CTD) and secondary RP to Systemic Sclerosis (SS).

According to the final clinical diagnosis made in later consultations (medium follow-up 2, 3 years), the patients were also assigned to three groups (primary RP, DCT and SS).

The sample included 286 subjects: 40 with SS pattern, 111 with probable CTD and 135 with primary RP.

The differences in these changes among the groups were very significant. In primary RP we observed more stasis (38.5%) and edema (35.6%), in CTD, serious dystrophies (89.2%) and in SS edema, and blurred capillary outlines in all the patients.

Tests for sensitivity, specificity and predictive values were high, as were the statistical levels among the various pathologies (Cohen K = 0.87).

We concluded that NCM criteria are an important tool for differentiating the etiology of RP.

Due to the high sensitivity, specificity, predictive value and statistical agreement levels, NCM is recommended as the first step test in the evaluation of patients with RP.

Key words: Scleroderma; Systemic Sclerosis; Nailfold capillary microscopy; Primary Raynaud's Phenomenon; Secondary Raynaud's Phenomenon.

INTRODUCTION

Raynaud's phenomenon (RP) can be the initial manifestation of many connective tissue diseases, including systemic sclerosis (SS) and Mixed Connective Tissue Disease (MCTD).[1]

RP is characterized by recurrent spasms of the arterial microcirculation of the fingers and toes, usually triggered by exposure to cold. It is manifested by a sudden pallor of the extremities, followed by reactive hyperemia and distal cyanosis. This is a phenomenon without any obvious underlying cause (primary RP or Raynaud's disease) or it may be associated with various situations (secondary RP), including connective tissue diseases, pathologies that we wish to focus on in this study.

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Distinguishing between primary RP and micro vascular changes in patients with secondary RP due to connective tissue diseases (CTD) is difficult. Objective measures are needed to help distinguish primary from secondary RP,[2,3] or to quantify the progression of the disease and possible response to treatment.

Effective tests for the differential diagnosis of RP, and prediction of the onset of other diseases, are not yet clear.[4]

Published studies addressing these issues include few patients, with widely varying follow-up times, which makes the interpretation and generalization of the results difficult.

When a patient presents PR, Nailfold capillary microscopy (NCM) is considered by many authors to be the essential test for guiding the diagnosis.[5] In fact, this test is able to detect early alterations in 90% of cases, long before the appearance of other clinical and biological signs of CTD. Moreover, several studies have found very high predictive values for NCM in RP.[4,6-9]

This technique has also been proposed as a simple

and very useful method of assessing the extent of involvement of the target organs in various diseases, particular, once again, in SS. [10,11]

Identifying patients with PR as an early and initial manifestation of a systemic alteration would be very interesting, not only for obtaining an early diagnosis, but also for predicting the prognosis. As a non-invasive method, NCM may be a good weapon for achieving this objective.[12-14] Many researchers believe that NCM should even be included as one of the diagnostic criteria for SS[15,16] and for various connective tissue diseases.[5,14,17]

To assess the value of this assumption and contribute to the differential diagnosis of these patients, the main objectives of this study are:

- To evaluate the most frequent capillary microscopic changes in patients with RP and their distribution according to the pattern recorded in the NCM.
- To analyze, in general, the informative value of different capillaroscopy criteria in these patients.
- To determine the validity of NCM in the differential diagnosis and screening of patients with RP.

MATERIAL AND METHODS

Retrospective evaluation was performed of the patients (n=286) diagnosed with Raynaud's phenomenon, aged between 15 and 65, seen for NCM in the Microcirculation Laboratory of the Medicine Service I of the Hospitals of the University of Coimbra over a nine-year period.

Only individuals were selected in whom the cause of RP was unknown at the time of the examination, and only the first observation was taken into account.

Patients taking medication that could interfere with the vascular system or induce RP were excluded, as well as patients with professions that could cause RP, and patients with carpal tunnel syndrome or ischemic disease.

Patients were divided into two groups, according to the capillaroscopy characteristics presented: primary RP or Raynaud's Disease, and secondary RP due to systemic diseases. The latter group was further divided into two other groups – one group with CTD, and the other with scleroderma.[18-20]

NCM was performed as a routine technique in our laboratory,[21] always by two different observers, who classified the nailfold microvascular changes during the examination and through photographs (4th finger of the left hand).

The following aspects were considered: number of capillaries per field; morphology of the capillaries (diameter and shape) and existence of intercapillary anastomoses; rheologic changes, particularly blood flow velocity and capillary motility; and the pericapillary appearance, in particular, the visibility of venules or the presence of pericapillary edema and spontaneous bleeding.

From the observations, three basic types of nailfold capillary pattern were identified:

Normal pattern – 10-12 capillaries/mm of skin, 200-250 µ in size, without tortuosities, branches, bleeding or pericapillary edema;

Transition or suspected pattern – capillaries in normal number, albeit smaller (<150 µ) with some tortuosities and dystrophies, but with a percentage of ≤60%/field.

Abnormal pattern – disorganized capillary loops, with reduced number of capillaries (<9/field), presence of severe branching, granular flow, pericapillary edema and/or bleeding.[22]

In cases in which the latter changes were more marked, with capillary counts of <6/mm or 9/field or extensive avascular areas (>1 mm) and in the presence of enlarged capillaries, the pattern was identified as *"Scledorema pattern"* according to the criteria already established by other authors.[18,23-26] In these cases, the capillary microscopic pattern was then classified as Early, Active and Late.

Transition or suspected patterns and abnormal patterns were designated as unclassified CTD.

Capillaries were morphologically classified according to their diameter, as normal, thin (<5 µ), enlarged (2 to 4 times the normal size, provided they are in two or more fingers, and 2 or more per finger) and giant capillaries (≥4 to 5 times the normal size) in at least two fingers. The dystrophic forms were also classified according to their degree of severity: moderate dystrophies or tortuosities and serious dystrophies; the latter includes giant capillaries.

Dystrophies considered severe were those exceeding 60% of all the capillaries observed per field.

The appearance of capillary *branches*, crossing over each other, was classified as anastomosis, i.e. disorganization of the capillaries.

The rheologic changes assessed were reduced blood flow (stasis) and decreased motility.

When observing the pericapillary appearance, the

following were recorded: visible venules, edema and spontaneous bleeding.

The rarefaction of thin capillaries and/or large avascular areas corresponded to areas of ischemia.

Following the examination, all the patients underwent further tests that led to a final diagnosis by their doctors. Based on the final diagnosis, the patients were then divided into three groups: primary Raynaud's phenomenon, connective tissue disease, and systemic sclerosis,[27,28] for comparison with the groups found by NCM.

The non-parametric data were analyzed by the *chi-square* test, and the quantitative data by analysis of variance – *Anova* – with repeated measurements (statistically significant value <0.05).

Sensitivity, specificity and predictive value of the test were calculated in relation to the final clinical diagnosis, for each patient group of patients.

To evaluate the validity and reproducibility of the NCM compared with all the other tests, the Cohen's Kappa test was used, considering a high probability value of between 0.8 and 1.0.

RESULTS

Of the 286 patients selected, in the observation by NCM, 40 (14.0%) showed a characteristic pattern of SS, 111 (38.8%) unclassified CTD, and 135 (47.2%) primary RP (Raynaud's phenomenon). Most were female (86.4%), and the female/male ratio was 6:1.

The mean age was higher among patients in the SS group (Anova p<0.008), ranging from 37.3±15.5 to 49.0±13.6 years.

The follow-up period of these patients was 2.3 (± 3.9) years on average.

Regarding the clinical characteristics of RP, the evolution time was longer in patients in the SS group, with significant differences among all the groups, ranging from 6.5±5.6 to 12.2±10.0 years, for CTD and SS respectively. The patients with primary RP showed a higher number of occurrences per year, although without statistical significance. The patients with the Scleroderma pattern had typical RP in 90% of cases, and 72.5% were positive in the cold stimulation test. The frequency of bilateral RP was higher than 90% in all situations.

Eight (20%) of the 40 patients classified in the SS group had an Early capillaroscopy pattern, 21 (52.5%) had an Active pattern, and 11 (27.5%) had a Late pattern,[18] meaning that more than half were already experiencing a serious pattern. Two of these patients were finally diagnosed with MCTD and other two with Raynaud's disease (these were classified as intermediate pattern - Active).

a) Alterations observed in the NCM

The capillary microscopic changes most frequently found in all patients were: capillary stasis (55.2%), followed by pericapillary edema (52.8%), serious dystrophies (41.3%), although with different distribution according to the classification into groups (*Table I*). All alterations showed very significant differences among the groups.

Patients with the "*Scleroderma*" pattern had more capillary microscopic alterations, showing, with an average of 9.3. The patients with unclassified CTD had, on average, 4.9 alterations each and the patients with primary RP had only 1.4 changes per patient.

The five most frequent capillary microscopic alterations reported in each group occurred in isolation in less than 38.5% of patients with primary RP. In the unclassified CTD group, the five most frequent alterations occurred between 89.2% and 45.9% of cases and, in the SS group, between 100% and 90% (*Table II*).

Comparing patients with Raynaud's disease and secondary RP (*Table III*), it was found that some alterations never occurred in patients with primary RP: severe dystrophies, avascular areas, reduced motility of capillaries, anastomoses, enlarged capillaries and areas with severe ischemia (known as *"deserted beach"*). These alterations occurred only in patients with secondary RP. The single most frequent alteration in primary RP was tortuous capillaries.

The alteration most frequently found in patients with primary RP was capillary stasis (38.5%). This was followed by pericapillary edema (35.6%) and tortuous capillaries (34.1%). Other abnormal aspects occurred in less than 8.1% of these patients.

The differences between the alterations found in primary and secondary RP were always highly significant for any parameter in the analysis.

In the unclassified CTD group, serious capillary dystrophies occurred in more than 89.2% of patients. Enlarged capillaries were observed in 6 patients. The remaining alterations always occurred in less than 61.3% of the patients.

When comparing the three groups, the differences

Table I

Changes observed in the Capillary Microscopy*

	Primary Raynaud's		Unclassified CTD		Systemic sclerosis		$\chi 2$	P	Total
	N	%	N	%	N	%			
Capillary stasis	52	38.5	68	61.3	38	95.0	42.5	0.001	158
Pericapillary edema	48	35.6	63	56.8	40	100.0	52.6	0.001	151
Serious dystrophies	0	0.0	99	89.2	19	47.5	200.7	0.001	118
Enlarged loops	7	5.2	61	55.0	34	85.0	115.1	0.001	102
Enlarged efferents	11	8.1	51	45.9	31	77.5	82.5	0.001	93
Blurred capillary outlines	9	6.7	41	36.9	40	100.0	127.2	0.001	90
Avascular areas	0	0.0	27	24.3	36	90.0	146.1	0.001	63
Tortuous capillaries	46	34.1	14	12.6	0	0.0	29.3	0.001	63
Reduced motility	0	0.0	14	12.6	26	90.0	176.2	0.001	50
Thin capillaries	11	8.1	34	30.6	4	10.0	23.4	0.001	49
Anastomoses	0	0.0	20	18.0	20	50.0	66.6	0.001	40
Enlarged capillaries	0	0.0	6	5.4	33	82.5	188.8	0.001	39
Ischemic areas	0	0.0	10	9.0	22	55.5	94.8	0.001	32
Visible venules	4	3.0	26	23.4	2	5.0	27.5	0.001	32
Spontaneous bleeding	2	1.5	12	10.8	18	45.0	58.8	0.001	32

Percentages relative to the total of patients per group

were statistically significant only for serious dystrophies, loops and enlarged efferents, thin capillaries, visible venules, tortuous and enlarged capillaries (*Table I*).

Enlarged capillaries were observed in 33 (82.5%) of the 40 patients with Scleroderma. All the patients showed pericapillary edema and blurred capillary outlines. Capillary stasis (95.0% of patients), reduction of capillary motility (72.0%), ischemic areas (90.0%) and enlargement of loops (85.0%) were also very common. Spontaneous bleeding occurred in 45.0% of cases.

All the capillary microscopic criteria in the SS group were statistically significant compared with the total of the same criteria found in patients with primary RP and CTD.

b) – Sensitivity and specificity of NCM

The results of the specificity and sensitivity test for NCM in relation to a differential diagnosis of RP were very significant in the diagnosis of primary RP, as the test was positive when the primary RP was diagnosed by capillary microscopy. The positive and negative predictive values were also high. Thus, between the diagnosis of primary and secondary RP, sensitivity was 88.5%, specificity was 97.1%, and the positive and negative predictive values were 97% and 88.7%, respectively. Between primary RP and the alterations that we call *unclassified* CTD, the sensitivity was 89.7%, the specificity was 96%, and the positive and negative predictive values were 97% and 86.5%, respectively. Between primary RP and SS, sensitivity was 98.5%, specificity was 100%, and positive and negative pre-

Table II

Most frequent capillary microscopic changes

Classification in groups by NCM	Capillary microscopic changes	% related to of patients per group
Primary Raynaud's n = 135	Stasis	38.5
	Edema	35.6
	Tortuous capillaries	34.1
	Enlarged efferents	8.1
	Thin capillaries	8.1
Unclassified CTD n = 111	Serious dystrophies	89.2
	Stasis	61.3
	Edema	56.8
	Enlarged loops	55.0
	Enlarged efferents	45.9
Systemic sclerosis n = 40	Edema	100.0
	Blurred outlines	100.0
	Stasis	95.0
	Avascular areas	90.0
	Reduced motility	90.0

dictive values 100% and 94.7%, respectively.

Similarly, specificity, sensitivity and predictive value tests for NCM related to the differential diagnosis of RP were very significant for the diagnosis of CTD (*Table IV*).

Comparing the capillary microscopy and final diagnosis (*Table V*), we found that 15 of all 151 patients initially classified by the NCM as having a secondary Raynaud's disease were ultimately diagnosed with Raynaud's disease.

Two of the patients with capillary microscopic appearance compatible with primary Raynaud's disease (135) had rheumatoid arthritis, one had systemic lupus erythematosus and one had MCTD.

Two of the patients classified with scleroderma pattern had connective tissue diseases and the cause of RP in other two patients has never been clarified, although they have had frequent RP attacks for about 12 years.

The concordance index (*Table VI*) for the various studied pathologies showed a significantly high value (0.87).

DISCUSSION AND CONCLUSIONS

The group of patients with secondary Raynaud's phenomenon (48.3% confirmed) in this study is quite similar to that found in hospital statistics, probably because it is a highly selected population, most of whom had already undergone previous screening by their physicians.

Cases of scleroderma pattern (14.0%) in which the diagnosis was confirmed (12.6%) were relatively high, but, once again, this is certainly because this is a population that has been screened previously.

The follow-up period for these patients was only 2.3 ± 1.5 years after performing NCM, which helps demonstrate the usefulness of the technique in the early differential diagnosis, taking into account that the PR in these patients had been evolving, in general, for around nine years and that the majority of patients with Scleroderma were already presenting severe injuries (Active and Late patterns).

As expected, the alterations found in NCM for these patients had very different frequencies, according to the classification group, but it was found that the presence of severe dystrophic forms, signs of ischemia, capillary anastomoses, decreased capillary motility, and enlarged capillaries were good criteria for predicting the existence of systemic diseases, as has been reported in other studies[29] as they were not present in any patient with primary RP. Even for the other parameters, there were very significant differences between the groups.

In line with several other studies,[30,31] we observed that the typical *"Scleroderma pattern"* changes in patients with secondary RP are different from those in the group which we refer to as unclassified CTD.

It should be noted that 82.5% of patients with scleroderma pattern had enlarged capillaries, compared to only 5.4% (6 patients) with unclassified CTD, possibly corresponding to patients with dermatomyositis. This fact is consistent with other studies,[32] where the presence of enlarged capillaries showed 100% sensitivity for Diffuse Systemic Sclerosis, 73% for Limited Sclerosis and 86% for Dermatomyositis.

The frequency of enlarged capillaries in our patients with SS was higher than in other studies[29] that consider NCM as a very specific test for this disease.

Ischemic areas, whether smaller or very extensive avascular areas, occurred in 90.0% and 55.5% of scleroderma cases, respectively. In patients with

Table III

Changes observed in the Capillary Microscopy*

	Primary Raynaud's		Secondary Raynaud's		χ^2	p	Total
	N	%	N	%			
Capillary stasis	52	32,9	106	67,1	30,1	0,001	158
Pericapillary edema	48	31,8	103	68,2	29,2	0,001	151
Serious dystrophies	0	0,0	118	100,0	177,1	0,001	118
Enlarged loops	7	6,9	95	93,1	101,8	0,001	102
Enlarged efferents	11	11,8	82	88,2	67,9	0,001	93
Blurred capillary outlines	9	10,0	81	90,0	71,6	0,001	90
Avascular areas	0	0,0	63	100,0	71,2	0,001	63
Tortuous capillaries	46	76,7	14	23,3	27,1	0,001	60
Reduced motility	0	0,0	50	100,0	53,4	0,001	50
Thin capillaries	11	22,4	38	77,6	14,1	0,001	49
Anastomoses	0	0,0	40	100,0	50,0	0,001	40
Enlarged capillaries	0	0,0	39	100,0	39,8	0,001	39
Ischemic areas	0	0,0	32	100,0	31,8	0,001	32
Visible venules	4	12,5	28	87,5	17,1	0,001	32
Spontaneous bleeding	2	6,3	30	93,8	23,9	0,001	32
Total alterations	190		919				

*Percentages relative to the total of each change observed

unclassified CTD, the frequency of these lesions was 24.3% and 9.0%, respectively.

Spontaneous bleeding was less common in patients with SS than in other series,[29] occurring in 45% of patients. However, it was considered statistically significant only in this pathology, which confirms its indicative value.

Severe capillary dystrophies were more frequent (83.9%) in the CTD group, and are probably the most specific sign we found for this disease. This will be the "*pattern*" for a suspected diagnosis of CTD.

In the "*Scledoderma pattern*", less than half of the patients had dystrophic capillaries.

We can say that the NCM, in the patients with primary RP, was practically normal, except for the presence of some stasis (38.5% of cases) and edema (35.6% of cases).

In our study, the "*Scleroderma pattern*" may include abnormal capillary microscopy aspects that were statistically significant in relation to unclassified CTD and primary RP. These aspects are: enlarged capillaries, enlargement of the loops and efferents, ischemic areas and spontaneous bleeding. The disorganization of capillaries which we call anastomoses was also frequent and significant in the "*Scleroderma pattern*". This pattern overlaps the previously-defined pattern, and is accepted in the practice of this technique.

This work does not subdivide patients with diffuse and limited scleroderma, as this division is not our objective. However, some authors[33] suggest the

Table IV

Valor diagnóstico da CPU para DTC não classificada e ES

Final Diagnosis			
NCM Diagnosis	**Systemic sclerosis**	**Unclassified CTD**	**Total**
Systemic sclerosis	36	2	38
CTD	0	96	96
Total	36	98	134
Sensitivity: 100.0%, Specificity: 98.0% , Positive predictive value: 94.7%, Negative predictive value: 100.0%			

Table V

Relation between capillary microscopy classification and final diagnosis

	Capillary microscopy diagnosis	**Final clinical-laboratory diagnosis**
Systemic sclerosis	40	36
Unclassified CTD	111	102
Primary Raynaud's	135	148

Table VI

Validity of nailfold capillary microscopy

		Nailfold capillary microscopy			
		Primary Raynaud's	**Unclassified CTD**	**SS**	
Final Diagnosis	Primary Raynaud's	131	15	2	148
	CTD	4	96	2	102
	SS	0	0	36	36
Kappa de Cohen = 0,87					

existence of predominant capillary microscopy characteristics in one or other type of SS, which would further contribute to the prognosis of this disease.

Despite being a highly selected population, this study confirms the very high sensitivity and specificity of NCM (always above 88.5% and 96%, respectively) in the identification of secondary microangiopathy in patients with RP, and also, of these, in the identification of RP in SS.

Our results are confirmed in other studies which, for example, even with inexperienced observers, reported sensitivities and specificities of 80% and 89%, respectively, in the differential diagnosis of Systemic Sclerosis and Rheumatoid Arthritis.[34]

In the group classified by NCM as "Scleroderma pattern", two patients ended up being diagnosed with idiopathic RP. This transition and Scleroderma pattern may have been caused by serious and persistent vasospastic phenomena, as these were patients with clinically severe RP.

The identification of these patients by NCM presenting secondary RP alterations should not be underestimated merely because the additional study was negative. This pattern should be regarded as an indicator of later development of CTD and, therefore, vigilance is always essential. This form of "*idiopathic*" RP should, therefore, be classified as "*suspected*" RP and can only be identified by capillary microscopy.

Raynaud's phenomenon should be investigated using an easy and non-invasive assessment, including the patient's history and clinical tests. In our opinion, these tests must include NCM, the value of which is shown by our results.

The predictive values of this technique for any of the diagnoses were always very high, with rates not less than 86.5%, according to the results already demonstrated in other studies.[32] The level of agreement between the NCM results and the final diagnosis was high.

For these reasons, it should be recommended that NCM be included among the diagnostic tests for Raynaud's phenomenon, since it identifies non-idiopathic forms, which are the only ones that need further investigation, saving unnecessary expense and inconvenience to many patients.

Thus, it is demonstrated by our results that NCM is a simple, non-invasive, low cost method, which should always be performed as the first step in the

evaluation of patients with RP. According to this statement, some authors consider NCM, or certain specific antibodies, as the most sensitive test for the differential diagnosis in Raynaud's phenomenon.

The technique also has an advantage over other techniques that the test can be repeated as many times as necessary, and the records of the images can be reviewed and compared at a later stage.

Due to the high sensitivity of this test, and as many researchers suggest,[20] we also propose that the capillary microscopy criteria, for some pathologies involving RP, including SS, should be an integral part of the *major* classification criteria and diagnosis accepted by the general consensus for these kinds of diseases. ■

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