A Practical Overview of the Role of Capillaroscopy in Rheumatic Diseases

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Abstract: Nailfold capillaroscopy is currently the best method to investigate microvascular abnormalities in systemic sclerosis and related conditions, and in other rheumatic conditions in which there is a clinical suspicion of microangiopathy. Although easy to perform, it is essential that the operators have been properly trained about correct method of images acquisition and interpretation. There are some parameters to indicate a normal/healthy capillaroscopic picture, but it is important to consider that there is a great variability in the capillary structure both interindividual and intraindividual. The early differential diagnosis between primary and secondary RP is the best advantage that the technique may offer.

Remarkable capillaroscopic alterations are found in the majority of cases of systemic sclerosis and the so-called "scleroderma spectrum disorders" (dermatomyositis, mixed connective tissue disease, undifferentiated connective tissue disease). Nevertheless, some capillaroscopic changes have been observed in systemic lupus erythematosus, Sjogren's syndrome, psoriatic and rheumatoid arthritis.

Discussion about controversies on this topic should be encouraged, leading to a progressive development of capillaroscopy as a routine investigation in rheumatology.

Keywords: Capillaroscopy, connective tissue diseases, Raynaud's phenomenon.

Capillaroscopy represents a "non-invasive" method of investigation of undisputed value in the recognition of morphological and functional microcirculatory abnormalities. Its use dates back to the beginning of the 20th century, but it was confined mainly to the experimental field until the 1980s. Since then, clinical applications of capillaroscopy have gradually expanded, especially in the field of rheumatology, to become an essential first-level examination for the differential diagnosis of primary and secondary Raynaud's phenomenon. The latter refers to a clinical manifestation that implies the presence of an underlying systemic disease. Among the diseases of rheumatologic interest, the more strongly linked to Raynaud's phenomenon is systemic sclerosis, even if it may appear also with other autoimmune diseases such as systemic lupus erythematosus, dermatomyositis, undifferentiated/mixed connective tissue disease.

The "*in vivo*" study of microcirculation takes place mainly at nailfold skin level. This is due to the fact that the major axis of the capillaries is parallel to the skin surface in this area, while in other areas, capillaries run perpendicular to the skin [1, 2].

Nailfold capillaroscopy can be carried out with various types of optical device, ranging from a simple magnifying glass to devices like the video capillaroscope with optical contact probes. The use of an ophthalmoscope or a dermatoscope represents the simplest method for a general and immediate assessment of the nailfold margin, albeit of low sensitivity due to the limited level of magnification (20x) [2,3]. A reflex camera equipped with good lenses offers an adequate panoramic view, while the stereomicroscope and the transmitted light optical microscope, with magnifications ranging from 10x to 100x, and ensure general observation and simultaneous analysis of detail of the single loops [2, 3]. In recent years, videocapillaroscopy with optical probes has opened new and original perspectives in the study of microcirculation, for the possibility of exploring both nailfold and non-nailfold skin [4]. The instrument can be equipped with software that uses algorithms for storing images and allow immediate printing for reporting.

Capillaroscopic examination must be performed on all fingers, correctly positioned with respect to the surface of the lens. The application of a drop of cedar oil on the skin to be explored makes it possible to obtain the best conditions of visibility of the capillaries. The examination should be carried out after a phase of "acclimatization" of variable duration, in relation to the difference between outdoor temperature and room temperature [1, 2].

The main parameters to be analyzed during capillaroscopic examination are skin transparency, visibility of the sub-papillary venous plexus, density,

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direction and spatial distribution of the loops, length and diameter of the capillaries, and flow characteristics [2, 3].

THE HEALTHY SUBJECT

In healthy subjects, the capillaroscopic picture is generally characterized by the morphological homogeneity of diameter, orientation and distribution of the capillaries, which look like an "inverted U" or "hairpin", arranged in a "comb" pattern, with a major axis running parallel to the skin surface (Figure **1**). The number of capillaries varies between 9 and 13 per mm and the morphological and structural characteristics of the nailfold microcirculation remain constant over time [2, 3]. The morphology of the capillaries and the architecture of the microvascular network can be very different among subjects, and this depends on several factors (age, gender, race, work activity), and even within the same individual, from finger to finger.

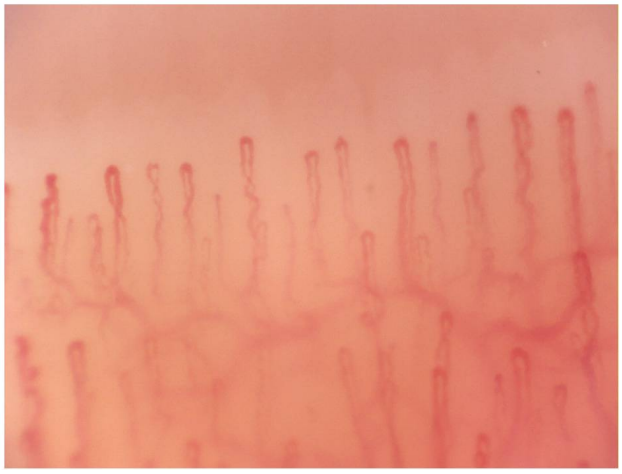

Figure 1: Healthy subject: nailfold capillaroscopic pattern.

Isolated abnormalities of distribution, morphology and orientation are not uncommon in the healthy subject, and their presence can be related to a wide range of conditions such as manicure, onychophagy, microtrauma and manual activities [2, 3]. Based on a cluster analysis, three morphologic patterns were described [5]:

1) the classic “normal pattern”, mainly with 2 to 5 U-shaped loops/mm and ≤ 2 tortuous loops/mm; 2) the “perfect normal” pattern with ≥ 5 U-shaped loops/mm; 3) the “unusual normal” with at least 1 meandering or bushy loop, or at least 1 microhaemorrhage, or with 4 crossed loops/mm.

Instead, if there is a microcirculatory impairment, there are marked alterations in the main capillaroscopic parameters, with significant changes in the orientation, morphology and spatial distribution of the loops that contribute to the disarrangement of the normal capillary architecture [3, 4].

THE SCLERODERMA MICROANGIOPATHY

The complex of alterations of the nailfold capillary network characteristic of systemic sclerosis and of the group of "scleroderma spectrum disorders" is called “scleroderma pattern”. There are various types of capillaroscopic expression regarding the scleroderma microangiopathy and these may coexist or manifest alone. Architectural disorder, the presence of homogeneous and/or uneven ectasias, microhemorrhages, marked expressions of capillary neoformation, and the reduction of the number of capillaries through to the appearance of avascular areas (no capillaries within an area > 500 microns) are the main elements that characterize the scleroderma microangiopathy (Figure **2A-D**) [6].

The scleroderma pattern can be observed in more than 90% of patients with systemic sclerosis, in about 75% of patients with dermatomyositis, in more than 50% of patients with mixed connective tissue and, to a lesser extent, in patients with undifferentiated connective tissue disease and with Sjögren's syndrome [2-5] (Table **1**).

Architectural derangement is an almost constant expression and its characteristics vary according to the stage of the diseases. In the early stages, it is characterized above all by the occurrence of normal capillaries alternating with regular and irregular dilated loops (Figure **3**). In the most aggressive forms, avascular areas and anarchic capillary neoformation accentuate the architectural disorder even more, creating situations that can be considered typical of the scleroderma microngiopathy (Figure **4**).

Based on the characteristics of the nailfold capillaroscopic pattern, the fundamental role of capillaroscopy in predictive assessment of the course of the disease has often been valued. The forms characterized by the presence of a marked increase in capillary diameter (microaneurysmatic ectasias, megacapillaries and irregular ectasias), without avascular areas, are typical of variants of the disease with a poorly evolving imprint, while the appearance of avascular areas characterizes the more aggressive forms [6].

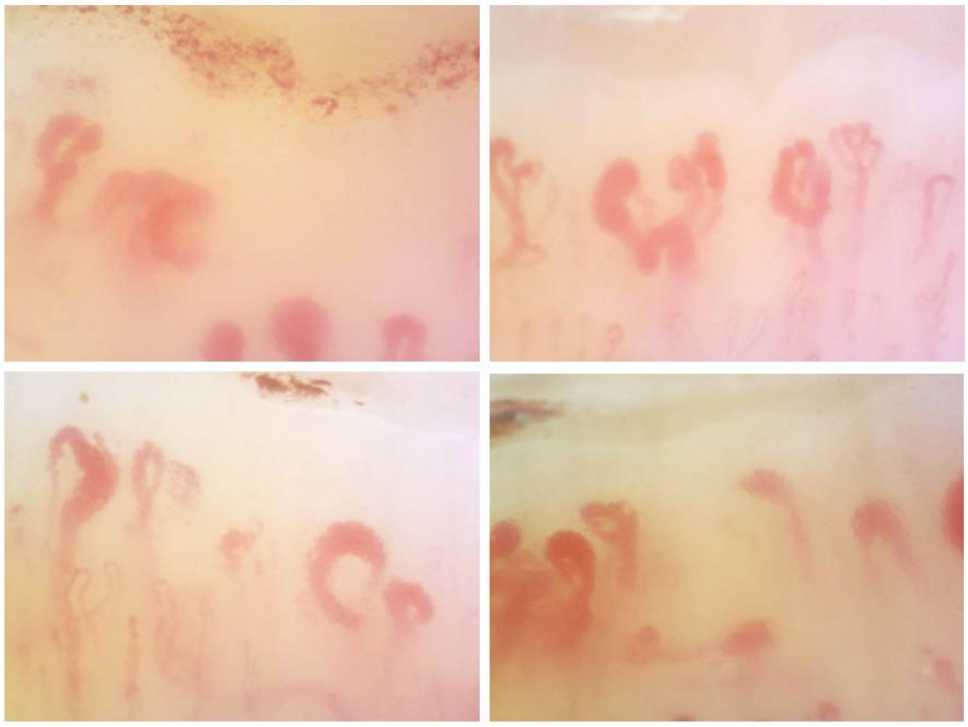

Figure 2: Specific capillary abnormalities of the scleroderma pattern: relevant architectural derangement with enlarged loops, branching capillaries, microbleedings and loss of capillaries.

Table 1: Capillaroscopic Abnormalities and Frequency of the "Scleroderma Pattern" in Connective Tissue Diseases

	Capillaroscopic pattern	Main abnormalities	% of patient's population with scleroderma pattern
Primary RP	Normal	/	/
Systemic sclerosis	Scleroderma pattern	Megacapillaries, irregular enlarged loops, microhaemorrhages, reduction in capillary density, avascular areas	>90
Dermatomyositis	Scleroderma pattern	Megacapillaries, irregular enlarged loops, micro-haemorrhages, neoangiogenesis	~70
Mixed connective tissue disease	Scleroderma pattern	Megacapillaries, irregular enlarged loops, microhaemorrhages, avascular areas	~50
Undifferentiate connective tissue disease	Scleroderma pattern	Megacapillaries, irregular enlarged loops	10-20
Sjögren's syndrome	If there is an overlap syndrome	Megacapillaries, irregular enlarged loops, reduction in capillary density	< 5
Systemic lupus erythematosus	If there is an overlap syndrome	Megacapillaries, irregular enlarged loops, reduction in capillary density	< 5

RP= Raynaud's phenomenon.

CAPILLAROSCOPY IN RHEUMATOLOGICAL DISEASES

Raynaud's Phenomenon

Nailfold capillaroscopy can be considered the first method used for the differential diagnosis between "primary" and "secondary" Raynaud's phenomenon.

In a patient with a clinically isolated Raynaud's phenomenon, the presence of one or more of the specific abnormalities of the scleroderma microangiopathy, even when limited to a single finger, should be considered indicative of a secondary nature, and justifies the simultaneous performance of further investigations, such as the detection of anti-nuclear antibodies [6].

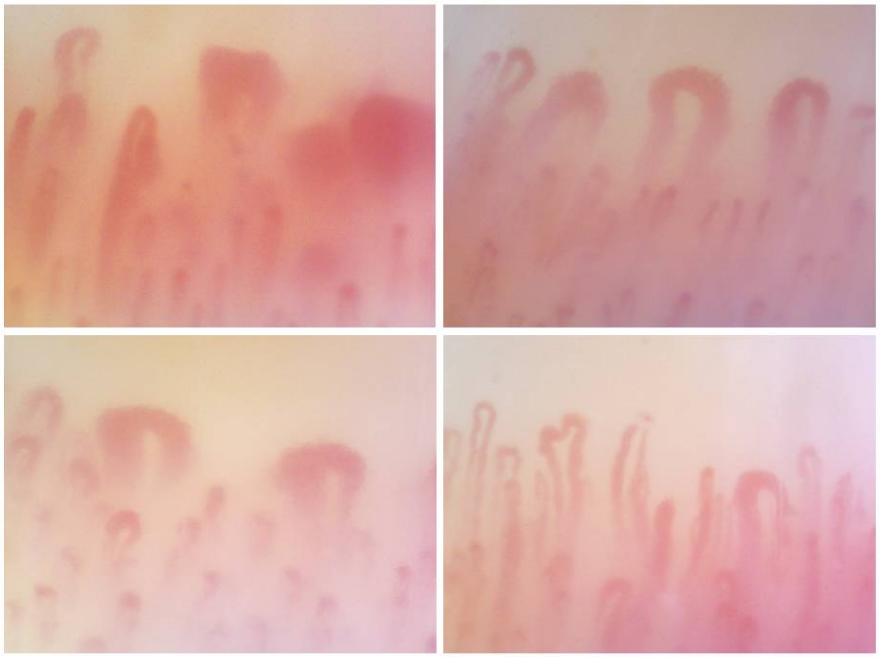

Figure 3: Scleroderma pattern: homogeneusly and inhomogeneusly marked enlarged loops.

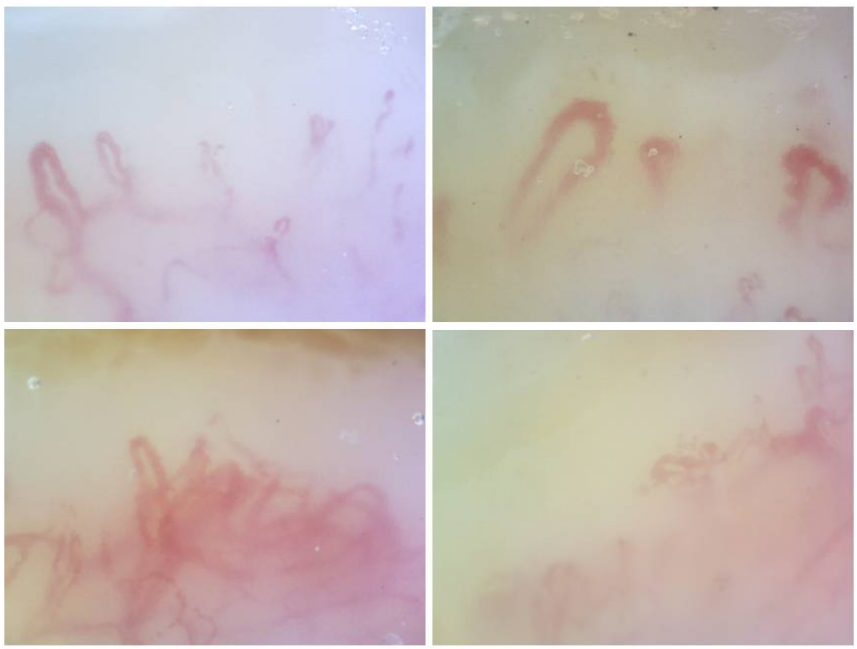

Figure 4: Scleroderma pattern: low skin transparency, loss of capillaries, avascular areas delimited by loops with relevant shape heterogeneity.

Capillaroscopic findings allow significant stratifications of the risk of evolution towards a "scleroderma spectrum disorder" within five years in subjects with isolated Raynaud's phenomenon, using a composite algorithm based on the presence of megacapillaries, microhemorrhages and the number of capillaries/mm [7]. The association of capillaroscopic abnormalities typical of the scleroderma pattern with the positivity of "specific" antinuclear antibodies (anti-centromere or anti-topoisomerase I) makes it possible to develop an additional predictive model capable of distinctly assessing the evolution towards systemic sclerosis [8].

Systemic Sclerosis

In scleroderma patients, a significant association between the severity of the skin involvement and/or

internal organs and capillaroscopic findings has been demonstrated. Patients with large avascular areas have an increased risk of "active" disease, of developing digital ulcers and of presenting a more significant skin, lung and cardiac involvement [9].

Capillaroscopy during systemic sclerosis is also used for prognostic purposes to identify patients with a high risk of developing digital ulcers or pulmonary arterial hypertension. In particular, the "quantitative" analysis of the single abnormalities at nailfold level (number of megacapillaries, maximum capillary diameter, and total number of capillaries) allows the construction of a highly specific and sensitive prognostic index capable of predicting the occurrence of digital ulcers [10].

Dermatomyositis

Dermatomyositis differs from polymyositis due to the substantial involvement of the microcirculation at skin and muscle level, and to the detection of capillaroscopic nailfold alterations in about 2/3 of subjects. Raynaud's phenomenon is frequent, in association with capillaroscopic nailfold abnormalities that can be similar on those of patients with systemic sclerosis (megacapillaries, irregular ectasies, microhemorrhages, neoangiogenesis, and derangement of microvascular architecture). Expressions of flourishing neoangiogenesis are frequently observed and may in some cases constitute the dominant capillaroscopic abnormality (Figure **5**). In patients with dermatomyositis, a particular microcirculatory environment has also been described, characterized by rapid changes in the morphology of the capillaries, which follow on from one another within the space of even just a few days [11, 12].

Mixed Connective Tissue Disease

The capillaroscopic pattern of mixed connective tissue disease can be very different, with expressions falling within the normal range or within manifest pathological pictures. Capillaroscopic alterations similar to those of scleroderma microangiopathy are detectable in more than half of all patients [13]. The presence of avascular areas is associated with pulmonary interstitial disease [13] and the detection of a scleroderma pattern seems to predict the development of pulmonary arterial hypertension.

Undifferentiated Connective Tissue Disease

Undifferentiated connective tissue disease is a condition in which there are signs and/or symptoms of systemic autoimmune disease that do not meet the classification and/or diagnostic criteria for "major" connective tissue disease. In most subjects, the capillaroscopic picture is normal. In some patients, especially if Raynaud's phenomenon is associated, it is possible to observe non-specific signs of microangiopathy, with a predominance of tortuous capillaries, homogeneous and inhomogeneous ecstasies [14]. In these cases, a capillaroscopic follow-

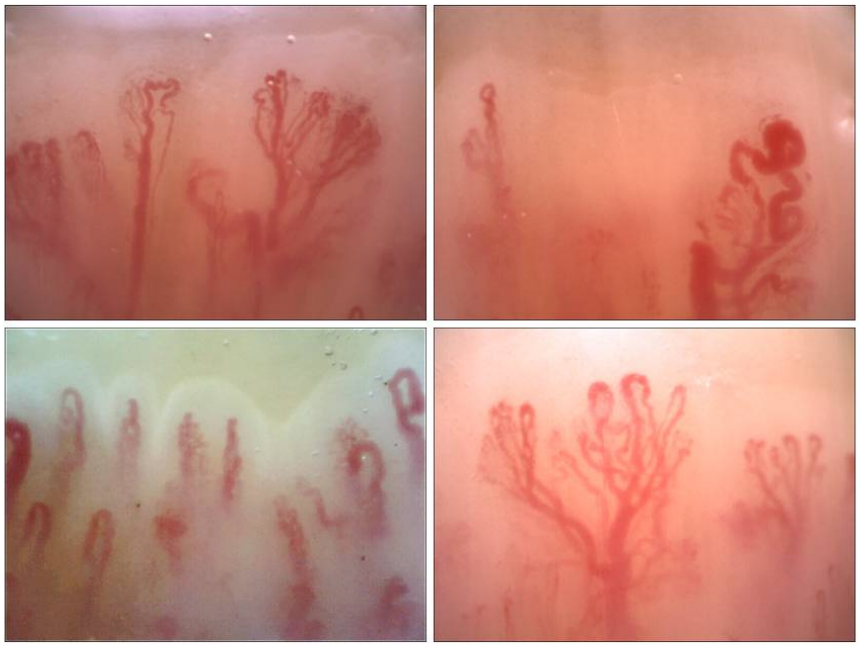

Figure 5: Dermatomyositis: architectural derangement of the nailfold capillary network with features of extreme angiogenesis.

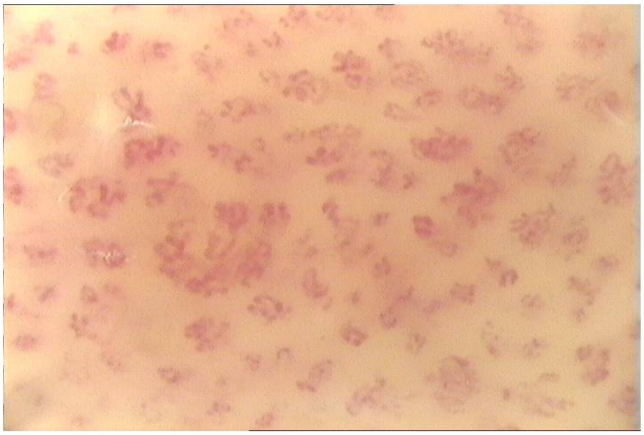

Figure 6: Capillaroscopy at the level of psoriatic plaque: tortuous, coiled balls, branching loops.

up seems appropriate in order to identify a possible evolution towards a major connective tissue disease, such as systemic sclerosis [15]. Some characteristic abnormalities of the scleroderma pattern can be observed in association with the simultaneous presence of anti-RNP antibodies and Raynaud's phenomenon [14].

Systemic Lupus Erythematosus

The capillaroscopic picture in patients with systemic lupus erythematosus is generally similar to that of the healthy subject. In about 1/3 of the patients, capillaroscopic abnormalities of uncertain significance have been described, including increased tortuosity, with loops that in some cases take on a meandering appearance, an increase in the length of the loops and greater visibility of the sub-papillary venous plexus [2, 3]. A well-recognized scleroderma pattern, on the other hand, is observed only in a small number of patients (5%), associated with Raynaud's phenomenon and anti-RNP antibodies [16].

Sjögren's Syndrome

In patients with Sjögren's syndrome, capillaroscopic alterations are unusual and, when present, are generally considered non-specific [17]. Some authors have observed reduced capillary density in presence of Raynaud's phenomenon or systemic manifestations of the disease. The presence of a scleroderma pattern is predictive of a possible evolution towards an "overlap" syndrome with systemic sclerosis [18].

Rheumatoid Arthritis

Patients with rheumatoid arthritis show no characteristic or representative alterations of microvascular damage. In most cases, capillaroscopic findings are similar to those of the healthy subject [19]. Sometimes, it is possible to observe thin and elongated loops, together with a marked visibility of the sub-papillary venous plexus, regarded in the past as a distinctive characteristic of a "rheumatoid" pattern. Now, these abnormalities are to be considered non-specific and by some as the probable expression of a concomitant steroid therapy [2, 3].

Psoriatic Arthritis

Nailfold capillaroscopy during psoriatic arthritis may reveal a series of non-specific abnormalities such as

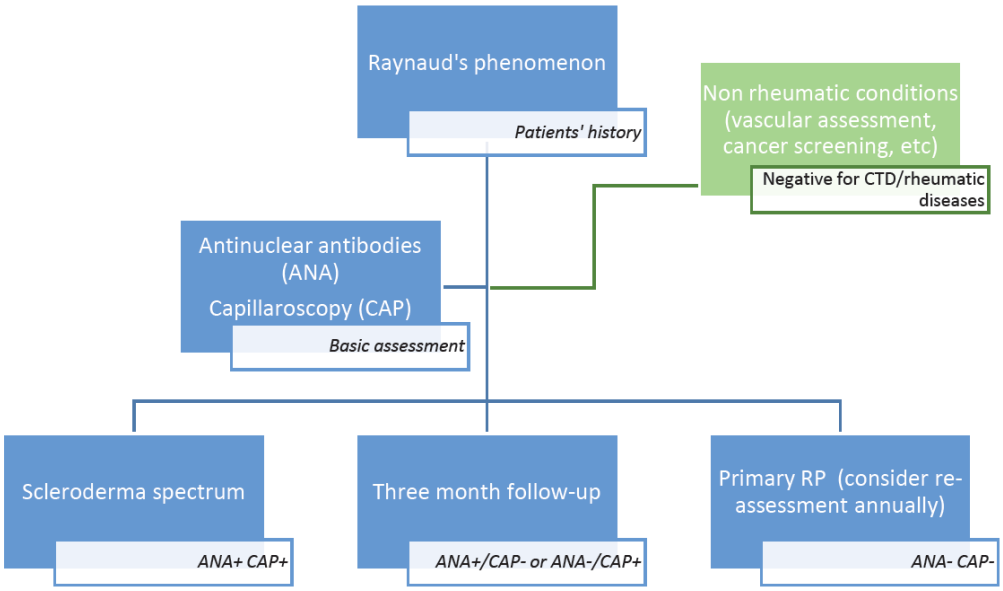

Figure 7: A simple algorithm for differential diagnosis of Raynaud's phenomenon.

microhemorrhages and reduction of capillary length ("dwarf" loops), the latter probably linked to a reduction in visibility secondary to hyperkeratosis [2, 3]. In the areas of the skin where psoriasis occurs, capillaries with a convoluted (ball-like) appearance are evident (Figure **6**), indicating a marked neoangiogenesis [20]. These alterations are reversible and may regress with the disappearance of psoriatic lesions [21].

CONCLUSIONS

Capillaroscopy is fundamental in distinguishing between primary and secondary Raynaud's phenomenon and has a prognostic value when combined with the presence of anti-nuclear antibodies (Figure **7**). The inclusion of capillaroscopic alterations in the classification criteria of systemic sclerosis has increased its sensitivity and allowed to identify early and incomplete forms of the disease [22]. In patients belonging to the scleroderma spectrum group (dermatomyositis, mixed connective tissue disease, undifferentiated connective tissue disease) the capillaroscopic picture may present great differences, and may fall within the normal range up to clearly pathological pictures. In patients with diseases not belonging to the group of scleroderma spectrum (systemic lupus erythematosus, Sjogren's syndrome), the presence of abnormalities typical of the scleroderma pattern must alert the clinician to the possibility of a full overlap with systemic sclerosis. In chronic arthritis (rheumatoid arthritis, psoriatic arthritis) the picture is mainly non-specific.

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