Nailfold capillaroscopic findings in primary Sjögren's syndrome: clinical and serological correlations

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Abstract

Objective

To describe the capillaroscopic abnormalities observed in patients with primary Sjögren's Syndrome (pSS), associating them with clinical and serologic features, and comparing these findings to those observed in normal controls.

Methods

Sixty-one consecutive patients with pSS were studied by clinical evaluation, serology, and nailfold capillary microscopy (NCM). Twenty-one normal controls were also examined. Capillaroscopic findings were recorded in a standardized way by a blinded observer. Capillary loss on NCM was evaluated using a deletion score.

Results

NCM was normal in 59.0% of pSS patients; 29.5% had non-specific abnormalities, and 11.5% presented a SD-like pattern. Patients presented a higher deletion score than controls ($p < 0.001$). Other capillaroscopic parameters (number of dilated, bizarre, and meandering capillaries; capillary hemorrhages; venous plexus visibility) did not differ significantly between patients and controls. Among patients, the deletion score was higher in those with systemic manifestations ($p = 0.022$) and Raynaud's phenomenon ($p = 0.050$). No association between the presence of antinuclear antibodies, rheumatoid factor, anti-SSA/Ro and anti-SSB/La with qualitative or quantitative NCM findings was found. Among the 7 patients with SD-like pattern on NCM, 6 had Raynaud's phenomenon, but only 2 presented autoantibodies related to systemic sclerosis (1 with anticentromere and 1 with low titer antitopoisomerase I). None of these patients met the ACR criteria for SSc.

Conclusions

SD-like pattern on NCM is observed in a small but significant proportion of pSS patients. The association of systemic involvement with a higher deletion score may be related to the hypothesis that these manifestations represent clinical expressions of systemic vasculitis.

Key words

Sjögren's syndrome; microscopic angioscopy; capillaries; xerostomia, keratoconjunctivitis sicca; antibodies, antinuclear; rheumatoid factor.

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Introduction

Primary Sjögren's Syndrome (pSS) is a systemic autoimmune disease which compromises mainly the exocrine glands (lacrimal and salivary glands). The disease can be associated with manifestations of vascular dysfunction, such as Raynaud's phenomenon (30%) and vasculitis (15-20%) (1, 2).

Nailfold capillary microscopy (NCM) is a non-invasive method which allows the assessment of the microcirculation by direct visualization of the nailfold distal capillary bed, contributing to differential diagnosis and prognostic evaluation of connective tissue diseases. The best described capillaroscopic pattern is the SD-pattern (from scleroderma), characterized by avascular areas and moderate to severe capillary dilatation, and often found in systemic sclerosis (SSc), dermatomyositis, and mixed connective tissue disease (3-6). In systemic lupus erythematosus (SLE), meandering, elongated, and tortuous capillaries are usually detected (6, 7). In dermatomyositis, exuberance of the SD-pattern and the presence of bushy capillaries are frequently observed (8-10).

There are only few studies in the literature describing capillaroscopic findings in pSS. In 1999 Tektonidou *et al.* described SD-like pattern in 12.5% of pSS patients with Raynaud's phenomenon (RP), and in 80% of those with anticentromere antibodies (all with RP) (11). Ohtsuka (12) observed greater capillary dilatation and tortuosity in patients with pSS than in controls.

The objective of this study was to identify capillaroscopic abnormalities in a series of patients with pSS, assessing the possible associations between NCM findings and the clinical features of this disease, as well as comparing them to those observed in normal controls.

Patients and methods

Patients and controls

From July 1999 through July 2003, 68 consecutive patients with primary Sjögren's syndrome seen at university hospital clinics (Hospital de Clínicas de Porto Alegre –HCPA– and Hospital São Lucas da PUCRS) and at a private rheumatology clinic were selected for this study. Patients were aged above 20 and met the 1993 Diagnostic Criteria from the European Community for pSS (13). Seven among these patients were excluded after the first assessment due to the following reasons: one patient met the ACR diagnostic criteria for SSc (14); one patient had associated rheumatoid arthritis; one patient had insulin-dependent diabetes mellitus; and four patients did not show up on the due date and time for their NCM. Patients with pSS were included no matter the period of time and/or activity of the disease. Patients with insulin-dependent diabetes mellitus, acute infections, neoplasias, serious chronic obstructive pulmonary disease, diffuse atherosclerotic disease, primary systemic vasculitis, congenital cardiopathy, or any other disease that might alter the peripheral rheological pattern were left out of this study. Patients who used to perform repetitive manual chores which might come to cause trauma in the periungual region, and patients with traumatisms in more than two digits, except for the thumbs, were not included in this study either. All patients signed written informed consent before entering this study, and the clinical protocol was approved by the Ethics Committee of the corresponding institution.

Twenty-one control subjects (recruited during the period of the study) aged above 20 were studied as a comparison group. None of them presented connective tissue diseases or major systemic illness.

Clinical assessment

A clinical assessment was performed by trained researchers according to a standardized protocol. Such protocol comprised questions referring to the onset and the course of the disease, to the presence of glandular and extraglandular manifestations, to lab tests results, biopsy, scintigraphy, radiological examinations, and therapies. Data were also obtained through the review of medical records. The parotid and submandibular glands were assessed by means of the scintigraphic method, using ^{99m}Tc. Related findings were ranked according to Fossaluza's (15) criteria. NCM and blood sample collec-

tion (for autoantibodies evaluation) were usually scheduled for 15 days after clinical assessment. Sera were stored at -20°C until all of them had been retrieved for analysis. Lab tests, radiological, and scintigraphic examinations, as well as histopathological tests were carried out inside the respective hospital departments from HCPA and Hospital São Lucas da PUCRS. Keratoconjunctivitis sicca was defined as the presence of xerophtalmia and objective evidence of dry eyes (positive Schirmer or Rose Bengal tests, or ophthalmological assessment diagnosing keratoconjunctivitis sicca) (16, 17). The occurrence of parotiditis was defined from pain to touch and/or increased volume of the parotid glands referred by the patient or noticed over clinical assessment. Raynaud's phenomenon was diagnosed from a history of intermittent episodes of paleness and/or cyanosis on exposure of extremities to cold.

Nailfold capillaroscopy

All capillaroscopies were performed by one of the authors (KGC), who was blinded for all clinical data from the majority (approximately 80%) of the patients. Eight digits from both hands, excluding the thumbs, were assessed making use of a Stemi 2000-C (Zeiss) stereomicroscope with 6.5-65x magnification equipped with a photographic camera (Contax167MT, Japan). Incident lighting at 45° was provided by a cold light source and a fiber optic illuminator. Cedar oil was deposited over the skin to allow visualization of the capillary bed. Room temperature was controlled and kept between 20° and 25°C (4). The areas of the nailfold region of the fourth digit from both hands were photographed in magnitudes of 10x and 25x, using photography film (Kodakcolor Gold ASA 400). The capillaroscopic findings of patients and controls were recorded in standardized form, using a protocol based on the model proposed by Andrade *et al*. (18). The occurrence of the SD pattern was qualitatively defined as the occurrence of avascular areas and/or the presence of enlarged capillaries, according to Maricq's (5) description. In addition, each microscopic variable was assessed (using a 10x magnification) and defined as follows. Deletion score: for each digit assessed in 10x, a deletion degree from 0 to 3 is established according to Lee's scale (0- absence of capillary deletion, 1- one or two discrete deletion areas, 2- more than two discrete deletion areas, 3- confluent areas of capillary deletion). Deletion area is defined as the loss of more than two successive capillaries in the distal row of the periungual region. The degrees assigned to each digit are added up and divided by the number of digits assessed, resulting in a deletion score (7, 18). A deletion score > 0.3 was deemed abnormal (18). Visibility index of the sub-papillary venous plexus (VISVP): a score ranging from 0 to 4 is assigned to each digit. VISVP is the sum of the scores assigned to each digit assessed (18). Mean number of periungual hemorrhages: micro-hemorrhages were counted in each digit, summed and divided by the number of fingers evaluated (18). The average number of ectasias (capillaries about 4x larger than the normal caliber), megacapillaries (capillaries about 10x larger than normal ones), meandering capillaries (novel-shaped), bushy capillaries (resembling arboreal formations), and bizarre capillaries (those not fitting any particular description), was obtained by counting them in all digits and dividing the total sum by the number of digits examined (18). The presence of tortuous and crossed capillaries as well as alterations of capillary bloodstream (granular or static flow) were also recorded (18).

Autoantibodies assessment

Sera of all the patients were assessed for antinuclear antibodies by indirect immunofluorescence on HEp2 cells (Nova Lite™ HEp2 ANA kit, Inova Diagnostics). The anti-SSA/Ro, anti-SSB/La, and antitopoisomerase-I tests were performed by ELISA (Quanta Lite™ SS-A, Quanta-Lite™ SS-B, and ™Scl70 Elisa kits, by Inova Diagnostics, respectively). The rheumatoid factor was detected by the turbimetry technique, with a Turbiquant® RF kit, of the brand Dade Behring.

Statistical analysis

The statistical analysis was performed with the statistical packages EPI-INFO (version 6) and SPSS for Windows (version 6). Comparisons comprising only categorical variables were performed by means of the chi-square test (with Yates correction) or Fisher's exact test. The quantitative variable with normal distribution was represented by mean and standard deviation (SD), and non-normal quantitative variables were represented by median and inter-quartile range (IQR). Mann-Whitney's test was used to test for associations involving quantitative variables with non-normal distributions. Values of $p \leq 0.05$ were considered statistically significant. All p values are two-tailed.

Results

Table I displays clinical and demographic characteristics of the patients and controls. Raynaud's phenomenon was seen in 30 patients (49.2%), and in 40% of them its symptoms preceded *sicca* syndrome. Sclerodactyly, ischemic lesions with tissue loss, "pitting-scars", digital necrosis or autoamputations were not observed. Non-erosive arthritis was observed in the majority of the patients. The prevalence of systemic manifestations is described in Table II.

Forty-three patients (70.5% of the cases) presented antinuclear antibodies, 35 of them with a fine speckled pattern. Cytoplasmatic patterns in IFI were observed in 10 patients (16.4%), with the mitochondrial pattern being the most frequent one (6 patients). Anti-Ro/SS-A and anti-La/SS-B were present in 33 (54.1%) and 27 (44.3%) of the patients, respectively (all patients with anti-La/SS-B also had anti-Ro/SS-A antibodies). Patients with anti-SSA/Ro antibodies had greater prevalence of systemic manifestations than other patients (72.7% versus 39.3%, respectively; $p = 0.018$), as did patients with anti-SSB/La antibodies compared to patients without these antibodies (74.1% versus 44.1%, respectively; $p = 0.037$). Thirty-nine patients (63.9%) were found to have rheumatoid factor. Anticentromere antibodies were detected in only one case. Low titers of anti-

Table I. Clinical and demographic characteristics of the patients and controls.

	Patients (n = 61)	Controls (n = 21)
Female sex – n (%)	59 (96.7)	18 (85.7)
Caucasians – n (%)	57 (93.4)	18 (85.7)
Age (years) – mean SD	49.2 ± 12.1	44.8 ± 13.4
Disease duration (years) – median (range)	9 (0.5-40)	
Xeroftalmia – n (%)	57 (93.4)	
Xerostomia – n (%)	56 (91.8)	
Keratoconjunctivitis sicca – n (%)	54 (88.5)	
Salivary gland enlargement – n (%)	29 (47.5)	
Parotid scintigraphy with Fossaluza score > 8* – n (%)	28 (45.9)	
Lower-lip biopsy with Chisholm-Mason III or IV† n (%)	7 (11.5)	
Raynaud's phenomenon – n (%)	30 (49.2)	
Non-erosive arthropathy – n (%)	52 (85.2)	
Systemic manifestations‡ – n (%)	35 (57.4)	

*47 patients had parotid scintigraphy. †8 patients had lower-lip biopsy. ‡Cutaneous or systemic vasculitis, hematologic, neurologic, pulmonary, or renal manifestations.

Table II. Systemic manifestations in 61 patients with primary Sjögren's syndrome.

	N	%
Peripheral neuropathy	10	16.3
Hematologic features (anemia, leucopenia, lymphopenia)	10	16.3
Systemic vasculitis	9	14.7
Cutaneous vasculitis	6	9.83
Other neurological features (optic neuritis, myelitis, encephalic vascular accident)	4	6.55
Pulmonary involvement (bronchiectasias, diffuse interstitial infiltration)	4	6.55
Renal tubular acidosis	1	1.63
Miscellaneous	3	4.91

Table III. Comparison of the capillaroscopic parameters between patients and controls*.

	Patients (n = 61) Median (IQR)	Controls (n = 21) Median (IQR)	p†
Deletion Score	0.0 (0.0–0.3)	0.0 (0.0–0.0)	< 0.001
VISVP‡	0 (0–2)	1 (0–4)	0.212
No. of meandering capillaries	0.5 (0.1–1.0)	0.3 (0.0–0.8)	0.200
No. of bushy capillaries	0.0 (0.0–0.1)	0.0 (0.0–0.3)	0.556
No. of ectasias	0.9 (0.0–1.5)	0.5 (0.1–0.8)	0.301
No. of capillary hemorrhages	0.0 (0.0–0.3)	0.0 (0.0–0.0)	0.105
No. of megacapillaries	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.107
No. of bizarre capillaries	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.404

* The number of each of the capillary abnormalities represents the total count divided by the number of digits examined. † Mann-Whitney test. ‡ VISVP: visibility index of the sub-papillary venous plexus.

topoisomerase I antibodies were detected in 5 patients: none of them presented a titer over 25 UI/ml (reference value is < 20 UI/ml).

Thirty-six patients (59.0%) had normal NCM, 18 (29.5%) had non-specific findings and 7 (11.5%) of them had capillaroscopic findings which characterize the sclerodermic or SD-like pattern. Among the 7 patients with SD-like pattern on NCM, 6 had Raynaud's phenomenon, but only 2 presented autoantibodies related to systemic sclerosis (1 with anticentromere, and 1 with low titer antitopoisomerase I). Among capillaroscopic alterations characterizing the non-specified pattern, an increased frequency of some atypical occurrences (bushy, bizarre and meandering capillaries) was observed. There was no significant difference in the prevalence of non-specific abnormalities in patients with and without Raynaud's phenomenon. None of the controls presented SD-like pattern on NCM, but 3 (14.3%) presented non-specific abnormalities.

The comparison of specific capillaroscopic parameters between patients and controls can be seen in Table III. The deletion score was higher in patients than in controls, but other characteristics did not differ significantly. The difference in the deletion score (higher value in patients) was still significant even when only patients without Raynaud's phenomenon where considered for analysis (p = 0.009). Megacapillaries were present in 7 patients, but in none of the controls (p = 0.182). Capillary hemorrhages were more prevalent in pSS patients (36.1% versus 19.0% in patients), although the difference was not statistically significant (p = 0.240). Capillary bloodstream abnormalities were observed in 25 (41.0%) patients with pSS (14 with granular bloodstream, and 11 with stasis), but were absent in controls (p = 0.001). The prevalences of other capillary abnormalities were not significantly different among patients and controls.

Less than half (44.3%) of the patients presented some degree of devascularization, i.e., a deletion score > 0. An abnormal deletion score (> 0.3) was detected in 11 patients (18.0% of the total), and only two patients presented deletion score > 1.0 (both with SD-like pattern). None of the controls presented a deletion score > 0.1.

The comparisons of the deletion score according to clinical and laboratory abnormalities are shown in Table IV. The deletion score was higher in patients with systemic manifestations than in the other patients. This difference is still statistically significant even when patients with SD-like pattern are excluded (p = 0.029). Raynaud's phenomenon was also associated with higher deletion scores. Patients with Raynaud's phenomenon (RP) had

Table IV. Comparison of the deletion scores according to the presence of selected clinical and serological abnormalities.

Abnormalities	Present		Absent		
	N	Median (IQR)	N	Median (IQR)	p*
Raynaud's phenomenon	30	0.1 (0.0 – 0.4)	31	0.0 (0.0 – 0.1)	0.050
Systemic manifestations	35	0.1 (0.0 – 0.4)	26	0.0 (0.0 – 0.1)	0.022
Vasculitis	17	0.1 (0.0 – 0.4)	44	0.0 (0.0 – 0.3)	0.116
Nuclear pattern on IFI†	43	0.0 (0.0 – 0.3)	18	0.0 (0.0 – 0.1)	0.287
Anti-Ro/SS-A	33	0.1 (0.0 – 0.3)	28	0.0 (0.0 – 0.2)	0.254
Anti-La/SS-B	27	0.0 (0.0 – 0.3)	34	0.0 (0.0 – 0.3)	0.076
IgM rheumatoid factor	39	0.0 (0.0 – 0.3)	22	0.1 (0.0 – 0.3)	0.253

* Mann-Whitney test. † IFI: Indirect Immunofluorescence (Hep-2 cells).

higher prevalence of extraglandular manifestations of the disease (62.9% versus 37.1% in patients without Raynaud's phenomenon; p = 0.026). Therefore, RP could possibly be a confounding factor to the association between systemic manifestations and deletion score. However, a trend in favor of the association between systemic manifestations and higher deletion score was present in patients with and without Raynaud's phenomenon, specially in the former group (P = 0.082). No associations were found between the presence of the antibodies studied and the deletion score.

Discussion

As far as we are aware of, this study of 61 patients with pSS is the largest of its kind performed to date that tries to relate clinical and serological findings on this disease with results obtained by standardized capillaroscopic assessment.

Unlike patterns described for systemic sclerosis and dermatomyositis (3-5, 9, 18), no specific capillaroscopic pattern can be defined for pSS. In a study of 22 patients with pSS and 30 with SLE, Ohtsuka (12) described his NCM findings among these patients without presenting any correlation whatsoever with clinical or serologic manifestations. Similar and non-specific findings were observed in patients with SLE and pSS such as slight increase in the capillary diameter and tortuousness. Tektonidou *et al.* (11) studied 40 patients with primary Sjögren's Syndrome (16 with and 14 without RP, and 10 with anticentromere antibodies and RP), a group of 40 normal controls, and 20 patients with systemic sclerosis. The authors observed altered NCM with non-specific findings in approximately half of patients and SD-like pattern in 10 (25%) patients (8 of which had anticentromere antibodies). Our study noted a lower prevalence of non-specific abnormalities (29.5%) and of SD-like pattern (11.5%). This difference might be due, at least partly, to the lower number of patients with anticentromere antibodies in this sample (only one case). If it weren't for the difference in the proportion of patients with anticentromere antibodies in both studies, the prevalence rates of the SD-like pattern would have been similar (approximately 10%). The non-specific findings observed in pSS by Tektonidou *et al.* comprised mainly tortuous and crossed capillaries and moderate visibility of the subpapillary venous plexus (11). However, in the present study we have not observed different prevalences of such characteristics in comparison to normal controls.

Among several capillaroscopic parameters tested in the present study, there was a significantly higher deletion score in patients than in controls. The number of capillary hemorrhages and megacapillaries tended to be higher in patients. These results parallel those found by Tektonidou *et al.* (11), in which a reduction in capillary density and higher prevalence of hemorrhages were observed in the group of patients with Raynaud's phenomenon. However, differently from Tektonidou *et al.*, we also found evidences of capillary loss in patients without Raynaud's phenomenon.

In this study, we have found an association between the existence of anti-SSA/Ro and anti-SSB/La antibodies and a higher frequency of systemic manifestations of pSS. These results confirm the conclusions reached by previous studies, which have shown associations between a higher frequency of extraglandular manifestations, specially vasculitis, and high titles of anti-SSA/Ro and anti-SSB/La (2, 19, 20). We are not aware of previous studies trying to associate the presence of clinical manifestations (besides RP) or the profile of antibodies with NCM findings. In the present study, no association between autoantibodies and findings in nailfold capillaroscopy has been found. However, we have observed that patients with systemic manifestations did present higher vascular deletion scores, regardless of the existence of a SD-like pattern. An explanation for this observation is the hypothesis that the systemic manifestations and the avascular areas in NCM represent clinical expressions of systemic vasculitis. We know that vasculitis can be detected in more than half of the patients suffering from pSS with systemic manifestations of the disease, specially in those presenting with purpura, peripheral neuropathy, nephropathy, obliterating endarteritis, and acute necrotizing vasculitis (1, 2, 19). Recent observations of avascular areas in patients with primary vasculitis (such as Wegener's granulomatosis and Behçet's disease) (21, 22) also corroborate the referred hypothesis.

The comparison of the deletion scores among patients with and without RP showed higher values in patients with Raynaud's phenomenon. Since Raynaud's phenomenon is also a clinical expression of the microvascular dysfunction that characterizes some connective diffuse diseases, these finding also express the systemic microangiopathy observed in pSS.

Nailfold capillary microscopy has been progressively more valued in the differential diagnosis and prognostic evaluation of Raynaud's phenomenon (23, 24). LeRoy and Medsger (25) have re-

cently proposed new criteria for the classification and diagnosis of systemic sclerosis (SSc), in which the presence of the SD pattern has been considered as one of the criteria for diagnosing this disease. Therefore, the observation of the SD-like pattern suggests that some patients with pSS might suffer from a type of microangiopathy similar to the one occurring in SSc. There is also a possibility that the appearance of SD-pattern represents an early phase in the course of SSc evolution, or even a type of disease which course is more benign within the spectrum of the SSc-related diseases. Only a prospective study, with a long term follow-up of these patients, will be able to answer these questions. On the other hand, there is evidence that patients with anticentromere antibodies present a potential risk of developing an overlapping syndrome with SSc (26, 27).

Finally, we have not found in this sample of patients with pSS any specific capillaroscopic pattern for pSS, what is in agreement with previous observations. However, patients with pSS with systemic manifestations presented higher deletion scores, suggesting that the devascularization noted in NCM is due to a vasculitis associated to the systemic involvement of the disease. It is also possible that NCM could identify some patients with overlapping syndromes with scleroderma spectrum diseases.

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