Microvascular abnormalities in Sjögren’s syndrome: nailfold capillaroscopy

M. Tektonidou, E. Kaskani, F. N. Skopouli and H. M. Moutsopoulos
Department of Pathophysiology, Medical School, National University, Athens and 1Harokopio University, Athens, Greece

Abstract

Objective. To describe microvascular abnormalities by nailfold capillaroscopy in patients with primary Sjögren’s syndrome (SS) with or without Raynaud’s phenomenon (RP) and those with anticientromere antibodies (ACA).

Methods. Forty patients with SS (14 without RP, 16 with RP, 10 with ACA), 20 patients with scleroderma (SSc) (10 with limited and 10 with diffuse disease) (disease control group) and 40 healthy controls (control group) were evaluated by nailfold capillaroscopy.

Results. Capillaroscopic abnormalities in SS ranged from non-specific findings (crossed capillaries) to more specific findings (confluent haemorrhages and pericapillary haemorrhages) or scleroderma-type findings. SS patients with RP presented capillary abnormalities in higher frequency than patients without RP. The majority of SS patients with ACA (80%) presented scleroderma-type findings.

Conclusion. Nailfold capillaroscopy can be used as a simple non-invasive method to evaluate the microvascular abnormalities in SS patients, especially in those with RP and those with ACA.

Key words: Sjögren’s syndrome, Nailfold capillaroscopy, Anticentromere antibodies, Raynaud’s phenomenon, Scleroderma.

The microvasculature may be affected in several connective tissue diseases. One manifestation connoting vascular dysregulation is Raynaud’s phenomenon (RP) [1]. Nailfold capillaroscopy is a non-invasive method of assessing skin microvasculature, contributing to the differential diagnosis and prognosis of several autoimmune disorders. The most characteristic capillaroscopic pattern, with prognostic value, is the scleroderma pattern [2]. In systemic lupus erythematosus (SLE), typical capillary findings have been detected [3]. Less specific capillary changes have been observed in other autoimmune disorders [4, 5]. In Sjögren’s syndrome (SS), nailfold capillaroscopy was carried out in the context of studying different connective tissue diseases [6]. One-third of SS patients present RP [7]. Recently, we described a group of SS patients with anticientromere antibodies (ACA) characterized by a low incidence of parotid gland enlargement, anti-La (SSB) antibodies and no clinical manifestations of scleroderma (SSc) besides RP [8].

The aims of the present study were (1) to investigate the microvascular abnormalities by nailfold capillaroscopy in patients with SS with and without RP, and to define possible differences between them (SS patients with ACA were also evaluated in order to investigate a possible distinct SS group) and (2) to compare the above abnormalities with the scleroderma pattern.

Patients and methods

Patients
Nailfold capillaroscopy was performed in 40 selective SS patients: 14 patients without RP, 16 age- and sex-matched patients with RP with a similar disease duration, and 10 patients with ACA. The diagnosis of SS was made according to the European classification criteria [9]. Nailfold capillaroscopy was also carried out in 20 age-matched patients with SSc: 10 with limited disease (ISSc) and 10 with diffuse disease (dSSc) (disease control group) [10], and in 40 age-matched healthy volunteers from the nursing and administrative personnel (control group).

The following data were taken from the patients’ files: presence of parotid gland enlargement, RP (diagnosed by careful history or observation of colour change on exposure of the extremities to cold), puffy hands, sclerodactyly, digital ulcers, telangiectasias, calcinosis (diagnosed by hand X-rays), oesophageal dysmotility
Capillaroscopy in Sjögren's syndrome

(470x842.0, 50x223)2. 'Non-specific findings': tortuous, crossed, bizarre similar frequencies in lSSc and dSSc. Two patients
Nailfold capillaroscopy and photomicrography were group or between groups, in regard to the frequency of
performed by the panoramic technique [11]. In this capillaroscopic abnormalities, were analysed using
Di
Nailfold capillaroscopy technique
Nailfold capillaroscopy and photomicrography were performed by the panoramic technique [11]. In this
study, qualitative and quantitative methods were applied. A millimetre ruler was photographed with the
same technique as used for nailfold photomicrographs. The capillary density was estimated as the mean number
of capillary loops/mm in the distal capillary row of the fourth and fifth finger on both hands [12]. All the other
parameters were measured on the nailfold of all 10 fingers. Besides the nailfold, the skin of the fingers and
hands was also examined for the presence of capillary or venular telangiectasias. The study was performed
blinded to disease group by the same investigator.
Classification of capillaroscopic findings
The classification was made according to Maricq [11] with some modifications. According to their size, the
nailfold capillaries were classified as normal, borderline, definitely enlarged and extremely enlarged. Capillary
loss was classified as slight, moderate and extensive [11], and the plexus visualization score (PVS) as low, moder-
ate and high [12]. Haemorrhages were classified in the following categories: (a) haemorrhages 1: less than two
punctate haemorrhages per finger; (b) haemorrhages 2: more than two punctuate haemorrhages per finger or
confluent areas of haemorrhages; (c) pericapillary haem-
orrhages. The morphological types of capillaries were the tortuous, crossed, bushy and bizarre capillaries [11,12]. Other observed capillaroscopic abnormalities were the thrombotic capillaries. Capillary and venular telan-
giectasias were also examined.
Capillaroscopic patterns
The above capillaroscopic findings were identified with the following patterns according to their clinical signifi-
cance, as previously described [2] with modifications.
We distinguished 'non-specific findings' from 'other findings' which are more specific.
1. Normal.
2. 'Non-specific findings': tortuous, crossed, bizarre capillaries, PVS (moderate and high), haemor-
rhages 1.
3. 'Other findings': haemorrhages 2, pericapillary haemorrhages, thrombotic capillaries.
4. Scleroderma-type findings:
(a) Active pattern:
Definitely enlarged capillaries.
Moderate or extensive capillary loss.
Bushy capillaries.
(b) Slow pattern:
Definitely or extremely enlarged capillaries.
None to slight loss.
Capillary telangiectasias.
(c) Overlap pattern: findings of both active and slow pattern.
Statistical analysis
The data were expressed as the mean ± s.d. The mean quantitative values were compared with Student’s t-test.
Differences between the patient groups and control group or between groups, in regard to the frequency of
capillaroscopic abnormalities, were analysed using $\chi^2$ or Fisher’s exact test. $P$ values of $\leq 0.05$ were considered
statistically significant.
Results
The demographic, clinical and laboratory findings of the SS and disease control patients are given in Table 1.
The control group consisted of 37 women and three men with a mean age of 54.3 ± 9.6 yr. The mean age,
disease duration (from first symptom), duration of sicca symptoms, and clinical and serological findings were
similar among patients with and without RP. All patients with SS and ACA had RP.
More than half of SS patients without RP had normal capillaroscopy. ‘Non-specific findings’ were observed in
42.8%, consisting mainly of tortuous, crossed capillaries and moderate PVS. These findings were also present in
32% of healthy individuals (Table 2): no significant differences between them were found. Only one patient
displayed haemorrhages (one and two simultaneously).
None had avascular areas or enlarged capillaries. The mean capillary density was not significantly reduced
(9.8 ± 1.5) compared to the control group (10.5 ± 1.1; $P = 0.09$).
In SS patients with RP, only two of the 16 patients had a normal pattern (12.5%). ‘Non-specific findings’
predominated (Table 2). A significantly higher percentage of crossed capillaries compared to the control group
($P = 0.005$) was noted. A higher percentage of moderate PVS and haemorrhages 1 compared to normals was
found, but this did not reach statistical significance ($P = 0.26, P = 0.64$, respectively). ‘Other findings’ were
significantly more frequent in this group compared to the control group: haemorrhages 2 were found in 31.2%
($P = 0.001$) and pericapillary haemorrhages in 18.7% ($P = 0.02$). The above abnormalities were not detected
in the control group. Haemorrhages 2 were found in similar frequencies in lSSc and dSSc. Two patients
displayed scleroderma-type findings. Both presented an active pattern. The mean capillary density (8.4 ± 2.0)
was significantly reduced compared to the control group ($P < 0.00001$), but significantly higher than
that observed in lSSc (6.5 ± 2.3) and dSSc (5.4 ± 1.5)
($P = 0.03, P = 0.0004$, respectively).
Comparing the capillaroscopic abnormalities between SS patients with and without RP, ‘non-specific findings’
and ‘other findings’ were found in higher frequency in
Table 1. Demographic, clinical and laboratory features of Sjögren’s syndrome patients and disease control patients

<table>
<thead>
<tr>
<th></th>
<th>Sjögren’s syndrome</th>
<th>Scleroderma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without RP*</td>
<td>With RP*</td>
</tr>
<tr>
<td>No. of patients</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Female:male</td>
<td>13:1</td>
<td>15:1</td>
</tr>
<tr>
<td>Age, mean ± s.d. (yr)</td>
<td>55.3 ± 7.4</td>
<td>54.6 ± 8.2</td>
</tr>
<tr>
<td>Duration of disease, mean ± s.d. (yr)</td>
<td>8.2 ± 5.4</td>
<td>8.0 ± 6.3</td>
</tr>
<tr>
<td>Duration of RP, mean ± s.d. (yr)</td>
<td>–</td>
<td>7.2 ± 6.3</td>
</tr>
<tr>
<td>Duration of sicca, mean ± s.d. (yr)</td>
<td>7.2 ± 6.0</td>
<td>6.3 ± 5.0</td>
</tr>
<tr>
<td></td>
<td>Per cent positive</td>
<td></td>
</tr>
<tr>
<td>Parotid gland enlargement</td>
<td>35.7</td>
<td>31.2</td>
</tr>
<tr>
<td>Puffy hands</td>
<td>7.1</td>
<td>12.5</td>
</tr>
<tr>
<td>Telangiectasias</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DLCO &lt;75%</td>
<td>0</td>
<td>6.2</td>
</tr>
<tr>
<td>Anti-Ro (SSA)</td>
<td>42.8</td>
<td>43.7</td>
</tr>
<tr>
<td>Anti-La (SSB)</td>
<td>21.4</td>
<td>18.7</td>
</tr>
<tr>
<td>Rheumatoid factor</td>
<td>50</td>
<td>56.2</td>
</tr>
</tbody>
</table>

RP, Raynaud’s phenomenon; ACA, anticytromere antibodies; DLCO, carbon monoxide diffusing capacity.

Table 2. Frequency of capillaroscopic findings (per cent positive) in Sjögren’s syndrome patients, disease control and control group, according to their classification in capillaroscopic patterns

<table>
<thead>
<tr>
<th></th>
<th>Sjögren’s syndrome</th>
<th>Scleroderma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without RP (n = 14)</td>
<td>With RP (n = 16)</td>
</tr>
<tr>
<td>Normal</td>
<td>57.1</td>
<td>12.5</td>
</tr>
<tr>
<td>‘Non-specific findings’*</td>
<td>42.8</td>
<td>65.2</td>
</tr>
<tr>
<td>Crossed</td>
<td>21.4</td>
<td>43.7*</td>
</tr>
<tr>
<td>Tortuous</td>
<td>35.7</td>
<td>37.5</td>
</tr>
<tr>
<td>Bizarre</td>
<td>0</td>
<td>6.2</td>
</tr>
<tr>
<td>Moderate PVS</td>
<td>21.4</td>
<td>31.2</td>
</tr>
<tr>
<td>High PVS</td>
<td>7.1</td>
<td>12.5</td>
</tr>
<tr>
<td>Haem 1</td>
<td>7.1</td>
<td>25</td>
</tr>
<tr>
<td>‘Other findings’*</td>
<td>7.1</td>
<td>31.2</td>
</tr>
<tr>
<td>Haem 2</td>
<td>7.1</td>
<td>31.2*</td>
</tr>
<tr>
<td>Per haem</td>
<td>0</td>
<td>18.7*</td>
</tr>
<tr>
<td>Thromb. Cap</td>
<td>0</td>
<td>6.2</td>
</tr>
<tr>
<td>Scleroderma-type findings</td>
<td>0</td>
<td>12.5</td>
</tr>
<tr>
<td>Slow pattern</td>
<td>0</td>
<td>12.5</td>
</tr>
<tr>
<td>Active pattern</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Overlap</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

RP, Raynaud’s phenomenon; ACA, anticytromere antibodies; PVS, plexus visualization score; Haem, haemorrhages; Per haem, pericapillary haemorrhages; Thromb. cap, thrombotic capillaries.

*P < 0.05 compared to the control group.

‘Several patients had more than one type of capillaroscopic finding.

RP-positive patients, although the difference did not reach statistical significance, perhaps because of the small number of patients: crossed capillaries (P = 0.26), haemorrhages 1 (P = 0.33), haemorrhages 2 (P = 0.17) and pericapillary haemorrhages (P = 0.21). The mean capillary density was significantly lower in patients with RP (P = 0.04).

All SS patients with ACA had pathologic nailfold capillaroscopy. Four out of 10 patients displayed ‘non-specific findings’, but not in a significantly higher frequency than the control group. ‘Other findings’ were found in a significantly higher frequency than normals: haemorrhages 2 were found in 50% (P < 0.0001), thrombotic capillaries in 20% (P = 0.03) and pericapillary haemorrhages in 40% (P < 0.0009). ‘Non-specific findings’ and ‘other findings’ were found in similar frequencies with those of lSSc. Eight out of 10 patients (80%) presented scleroderma-type findings; five out of eight had slow pattern. The mean capillary density (mean density 7.2 ± 1.6) in this group was significantly lower compared to the control group (P < 0.00001), but it was not significantly different from that found in lSSc (P = 0.44). The mean capillary density in dSSc was significantly lower than in SS patients with ACA (P = 0.01).

Discussion

In this study, using qualitative and quantitative methods of nailfold capillaroscopy, the microvascular abnormalities in SS patients with or without RP, as well as patients with ACA, were evaluated. ‘Non-specific find-
Involvements were distinguished from the ‘other findings’ which were more specific. ‘Non-specific findings’ have been found in patients with several connective tissue diseases, as well as in healthy individuals. ‘Other findings’ have predominantly been described in scleroderma and SLE patients, and were not present in the normal population [13].

In SS patients without RP, normal and ‘non-specific findings’ were predominant. The mean capillary density was not significantly reduced compared to normals. On the other hand, SS patients with RP presented ‘non-specific findings’ (crossed capillaries) and ‘other findings’ (confluent haemorrhages and pericapillary haemorrhages) in significantly higher frequency than the control group. The mean capillary density in patients with RP was also significantly lower than that in RP-negative patients. Two patients with RP also displayed scleroderma-type findings. The first patient had active disease with extensive parotid gland enlargement, peripheral neuropathy and periungual erythema. The second patient presented mild periungual erythema. Scleroderma-type abnormalities have also been found in SLE patients with periungual diskoid lesions [14].

Most studies, investigating the capillaroscopic findings of several autoimmune diseases, did not state whether patients with RP differ from those without RP. Some authors noted no significant differences in nailfold capillaroscopy among RP-positive and RP-negative patients [15]. Others demonstrated an increase in mean capillary diameter and a decrease in the capillary number of the first capillary row, associated with the frequency and severity of RP attacks [16]. Besides the classic mechanisms of vasospasm, the digital artery and microvascular lesions may play a role in the pathogenesis of secondary RP, and may explain the different capillaroscopic findings in RP-positive SS patients.

SS patients with ACA were also investigated. In a previous study, SS patients with ACA and RP, without telangiectasias, calcinosis, sclerodactyly and a low incidence of parotid gland enlargement and anti-La (SSB) autoantibodies, were described [8]. The question of whether this group of patients constitutes an overlap between ISSc and SS was raised. In this study, all the patients had a definite diagnosis of SS. Their predominant features were sicca manifestations and RP (Table 1). Some of them had clinical features similar to CREST, but none fulfilled the three out of five ACR criteria for the syndrome [10]. Two out of 10 patients had telangiectasias. More than half the patients had puffy hands (60%). None presented sclerodactyly, facial scleroderma, digital ulcers, oesophageal dysmotility or calcinosis. A low incidence of parotid gland enlargement, anti-Ro (SSA) and anti-La (SSB) antibodies in comparison to other SS patients was observed (Table 1). Nailfold capillaroscopy showed scleroderma-type findings in eight out of 10 patients. A slow pattern predominated in these patients, such as in ISSc (Table 2). ‘Non-specific findings’ and ‘other findings’ were described in similar frequencies with those of ISSc patients. The mean capillary density was also similar to that found in ISSc.

In several previous studies of idiopathic RP, the presence of ACA was highly indicative of future development of CREST syndrome or ISSc [17]. Le Roy et al. [18] have proposed that patients with RP, ACA and scleroderma pattern in capillaroscopy should be included in the spectrum of ISSc, although no cutaneous scleroderma was observed. In our patients, RP was predominant, but sicca symptoms and generally clinical and serological features of SS were present simultaneously. Our findings are highly suggestive that the SS-ACA group can be included under the umbrella of ISSc, even though it does not have clinical manifestations of this disease in a 10 yr follow-up. The time of ISSc diagnosis varies among individuals and it is possible that some patients may present an atypical form of the disease for years. The slow pattern in this group of patients may be related to slow evolution to the limited form of SSc. Since the presence of ACA in SS may serve as an early predictor of ISSc, further evaluation by nailfold capillaroscopy and close follow-up should be performed.

In conclusion, SS patients, and especially those with RP, present capillaroscopic abnormalities ranging from non-specific to more specific findings or, on some occasions, scleroderma-type findings. The majority of patients with SS and ACA present scleroderma-type findings and probably constitute an overlap with a subclinical form of ISSc.

References


