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Prevalence and evolution of scleroderma pattern at nailfold videocapillaroscopy in systemic sclerosis patients: Clinical and prognostic implications ☆

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ABSTRACT

Background: Microvascular involvement plays a decisive role in systemic sclerosis (SSc) pathogenesis occurring early in the course of the disease. Microangiopathy is responsible of important clinical manifestations, such as Raynaud's phenomenon, digital ulceration, and pulmonary arterial hypertension. Typical microvascular alterations, called scleroderma pattern, are detectable at nailfold capillaroscopy in a significant percentage of SSc patients; however its prevalence is highly variable in published studies.
Aim: The aims of this study are to evaluate the prevalence and the evolution of scleroderma pattern in SSc patients and analyze their demographic, clinical and prognostic characteristics according to capillaroscopic features.
Methods: Two hundred and seventy-five SSc patients, underwent at least two nailfold videocapillaroscopy during follow-up, were retrospectively enrolled.
Results: A scleroderma pattern was observed in 80% of patients at baseline and 87.1% during follow-up, and it was significantly associated to digital ulcers, interstitial lung disease, reduction of diffusion lung of carbon monoxide <75%, teleangectasias and melanodermia, while sicca syndrome and arthralgias were associated to normal/nonspecific pattern. Digital ulcers, teleangectasias, sicca syndrome, and arthralgias remained independently associated with scleroderma pattern on multivariate analysis.
In conclusion, the main clinical manifestation correlated with scleroderma pattern is the occurrence of digital ulcers, and their appearance is strictly correlated with the variation of capillaroscopic feature during the time. Further studies should confirm the association between SSc pattern and lung fibrosis.

Introduction

Systemic sclerosis (SSc) is a connective tissue disease characterized by endothelial dysfunction, dysregulation of fibroblasts with collagen overproduction, and complex immune system abnormalities (Avouac et al., 2011; Ferri et al., 2014). A frequent consequence of this chronic disease is the multiple organ damage/failure responsible for marked impairment of the patient's quality of life and increased mortality (Avouac et al., 2011; Ferri et al., 2014). Vascular involvement plays a decisive role in SSc pathogenesis occurring early in the course of disease, typically with the appearance of Raynaud's phenomenon (Kahaleh, 2004). Microangiopathy is also directly responsible for some severe clinical manifestations, such as digital ulceration, pulmonary arterial hypertension and scleroderma renal crisis (Lambova and Müller-Ladner, 2010).

Capillaroscopy is an imaging technique, for the in vivo study of microcirculation, quick to perform, non-invasive, and not expansive (Grassi and De Angelis, 2007; Ingegnoli et al., 2013a). The first description of capillary abnormalities in systemic sclerosis (SSc) dates back to 1925 by Brown and O'Leary (1925) and these findings were thereafter called 'scleroderma pattern'. In the last 3 decades many authors have investigated the scleroderma microangiopathy, and now the capillary abnormalities in SSc are well documented (Grassi and De Angelis, 2007; Ingegnoli et al., 2013a; Smith et al., 2012, 2013).

Recently, the presence of a scleroderma pattern has been included in classification criteria for SSc (van den Hoogen et al., 2013), but although it is detectable in a significant percentage of SSc patients, the prevalence of scleroderma pattern is highly variable in published studies (Bergman et al., 2003; Cutolo et al., 2006; Lambova and Müller-Ladner, 2011; Nagy and Czirják, 2004).

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The aims of the study were to evaluate the prevalence and evolution of scleroderma pattern in a large cohort of SSc patients and analyze their demographic, clinical and prognostic characteristics in relation to the capillaroscopic features.

Methods

Patients

Two hundred and seventy-five SSc patients, referred to our Rheumatologic Centre from February 2005 to October 2014, classified according to 2013 criteria (van den Hoogen et al., 2013), were retrospectively enrolled. All patients who underwent at least two nailfold videocapillaroscopy (NVC) during follow-up were enrolled in the study. Demographic, clinical, and serological data were collected for all patients at any NVC time. To calculate survival rates the vital status of all patients was established at the end of the study.

Standardized criteria were followed for the evaluation of clinico-epidemiological parameters. In particular, we defined:

1) SSc duration: the age at disease onset was considered to be the age at which the first signs and symptoms compatible with the disease, different by Raynaud, appeared; namely, digital ischemic lesions, puffy hands, sclerodactyly with or without proximal scleroderma, dyspnea, and/or dysphagia (Ferri et al., 2014);
2) cutaneous subsets: patients were classified as having limited cutaneous scleroderma (sclerosis of distal extremities, not above the elbow and knees, with or without sclerosis of neck and face) or diffuse cutaneous scleroderma (sclerosis of both distal and proximal extremities, with or without truncal involvement). Patients with sine scleroderma SSc were invariably included in the limited cutaneous SSc subset (Ferri et al., 2014);
3) autoantibodies: antinuclear and antinucleolar antibodies were detected by indirect immunofluorescence on Hep-2 cell lines (dilution 1:80); anti-extractable nuclear antigen antibodies, including anti-Scl70, and anti-CENP, were detected by ELISA technique (Catoggio et al., 1983; Ferri et al., 2014; Steen et al., 1988).

Nailfold videocapillaroscopy

NVC was performed, according to standard technique, with a videocapillaroscope equipped with a 200× optical probe (Videocap 9.07 software; Videocap 3.0 from 2011; DS-Medica, Milan, Italy). Images were saved and retrospectively evaluated in a blind manner by two operators with respect to clinical status of patient. Few cases of disagreement about the presence of scleroderma pattern were resolved by consensus. NVC pattern was considered negative when it showed normal or nonspecific alterations (Fichel et al., 2014).

Normal NVC pattern was defined as a regular disposition of the capillary loops along the nailfold bed and no abnormal enlargement or capillary loss (De Angelis et al., 2009). Nonspecific NVC pattern was defined as the absence of giant capillaries with focal distribution of microhemorrhages and/or minor capillary morphological changes (meandering and crossed capillaries) or isolated ramified capillaries (Ingegnoli et al., 2013b). Scleroderma pattern was defined as the association of giant capillaries and microhemorrhages or the association of bushy capillaries, microvascular array disorganization and capillary loss or avascular areas (Bukhari et al., 2000; Cutolo et al., 2000; Ingegnoli et al., 2013b; Sebastiani et al., 2009).

Statistical analysis

Categorical variables were analyzed by chi square test or Fisher's exact test and differences between the means were determined using Mann–Whitney test for unpaired samples. P values ≤ 0.05 were considered statistically significant. Cumulative survival rates were computed by the Kaplan–Meier method, and the difference between survival curves by the Mantel–Cox (log-rank) method (Altman, 1991).

Results

Two hundred and twenty patients (80%) showed a scleroderma pattern at the moment of the first evaluation (group 1) (Fig. 1), while in 55 patients (20%) scleroderma pattern was not observed (group 2). Among group 2, 23 (41.8%) showed nonspecific alterations, while NVC was normal in the remaining 32 patients (58.2%).

Main clinical, serological and demographic features of the 275 SSc patients enrolled in the study are reported in Table 1.

No significant differences were observed for mean age at diagnosis, mean disease duration, extension of skin involvement and autoantibodies profile between the two groups. On the contrary, patients of group 2 had an older age at Raynaud's phenomenon onset ($p = .019$) and a lower prevalence of male gender (only 2 males, $p = .02$). Digital skin ulcers, interstitial lung disease at high resolution computed tomography and a reduction of diffusion lung of carbon monoxide (DLco) <75% were significantly more frequent in group 1 ($p < .0001$, $p = .047$, and $p = .023$, respectively). Although rare, scleroderma renal crisis was observed only in patients of group 1. Moreover, group 1 showed more frequently teleangectasias ($p = .009$) and melanodermia ($p = .028$), and a lower frequency of sicca syndrome ($p = .015$), and arthralgias ($p = .012$). No differences between the two groups were recorded about ongoing treatments at the time and before the first NVC.

Digital ulcers (odds ratio [OR] 0.31, 95%-confidence interval [CI] 0.1–0.96, $p = .043$), teleangectasias (OR 0.34, 95%-CI 0.16–0.73, $p = .006$), sicca syndrome (OR 2.36, 95%-CI 1.09–5.08, $p = .028$), and arthralgias (OR 2.11, 95%-CI 1.00–4.42, $p = .049$) remained independently associated with normal/nonspecific pattern on multivariate analysis.

Finally, group 1 had a 10th-year mean survival of 80.1%, while the mean survival of group 2 was 85.5%, without significant differences.

NVC evolution

During the follow-up the NVC features (appearance or regression of scleroderma pattern) changed in 29/275 (10.5%) SSc patients, while 246/275 (89.5%) showed a stable NVC pattern.

In particular, a normalization of NVC features was observed in 13/220 (5.9%) patients of group 1, while a scleroderma pattern appeared during the follow-up in 16/55 (29.1%) patients of group 2 (Fig. 1). These latter showed at baseline a nonspecific pattern in

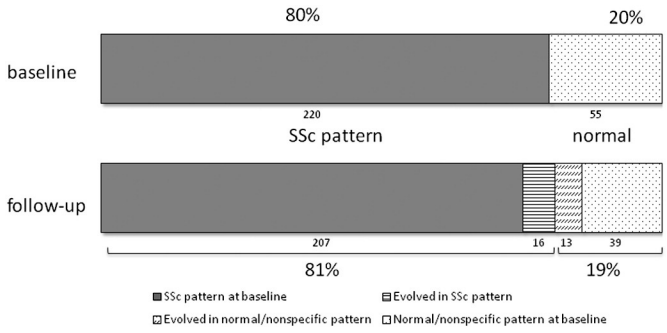

Fig. 1. Rate of scleroderma pattern at baseline and during follow-up in 275 systemic sclerosis patients.