Autoimmunity Reviews 16 (2017) 787–795

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

The role of nailfold capillaroscopy in the assessment of internal organ involvement in systemic sclerosis: A critical review

Stergios Soulaidopoulos [a], Eva Triantafyllidou [a], Alexandros Garyfallos [a], George D. Kitas [b], Theodoros Dimitroulas [a,*]

[a] Fourth Department of Internal Medicine, Hippokration University Hospital, Medical School, Aristotle University of Thessaloniki, 49 Konstantinoupoleos Street, 54642 Thessaloniki, Greece
[b] Arthritis Research UK Centre for Epidemiology, University of Manchester, Oxford Road, Manchester, M13 9PT, UK

ARTICLE INFO

Article history:
Received 25 April 2017
Accepted 1 May 2017
Available online 30 May 2017

Keywords:
Nailfold capillaroscopy
Systemic sclerosis
Pulmonary hypertension
Interstitial lung disease
Atherosclerosis

ABSTRACT

Endothelial dysfunction and microvascular damage constitute the hallmarks of systemic sclerosis (SSc), explaining much of the pathophysiology and clinical manifestations of the disease. Nailfold videocapillaroscopy (NVC) is an established method for the assessment of the microvasculature, aiding in distinguishing different types of structural vascular abnormalities. Until recently, NVC was used in the diagnosis of SSc as well as in the assessment and follow-up of peripheral digital vasculopathy. On the top of digital ulcers, internal organ involvement such as myocardial dysfunction, pulmonary vascular and/or parenchymal lung disease characterizes severe SSc imparting a high risk of mortality. There is growing evidence suggesting that the extent of peripheral microvascular changes reflects the severity of the disease, especially in terms of life-threatening cardiopulmonary complications. The possible use of nailfold videocapillaroscopy as a useful, non-invasive modality to improve the ability to identify patients at higher risk for these devastating complications of the disease remains to be established.

The aim of this review is to critically summarize and discuss current literature regarding the relationship between morphological alterations of nailfold dermal papillary vessels and several manifestations of SSc, focusing on visceral organ involvement, as well as their association with surrogate markers of macrovascular disease.

Contents

1. Introduction

Systemic Sclerosis (SSc) is a rare multisystem connective tissue disease characterized by microvascular damage, extensive fibrosis of the skin, immune dysregulation and progressive impairment of internal

* Corresponding author at: 4th Department of Internal Medicine, Hippokration Hospital, 49 Konstantinoupoleos Street, Thessaloniki 54642, Greece.
E-mail addresses: dimitroul@hotmail.com, dimitroul@auth.gr (T. Dimitroulas).

http://dx.doi.org/10.1016/j.autrev.2017.05.019
1568-9972/

organ function [1]. Women are affected more frequently than men (3:1–4:1) and symptoms usually appear in the third to fifth decades of life [2]. Two forms of the disease are generally recognized based on the extent of skin involvement: diffuse cutaneous (dcSSc) and limited cutaneous SSc (lcSSc). In dcSSc skin changes extend to the trunk and proximal extremities and are commonly followed by rapidly progressive fibrosis of the lungs, heart and other internal organs, whistle in the limited type, skin fibrosis is mainly restricted to distal extremities and face [3].The course and prognosis of SSc are mainly determined by the extent and severity of internal organ involvement and particularly cardiopulmonary complications which represent the leading causes of death in this population [4,5]. Given the silent presentation of heart and lung disease which gradually progresses to advanced stages, early identification of specific subgroups of SSc individuals at higher risk for cardiopulmonary involvement is highly desirable but remains an unmet need in routine clinical practice [6].

The precise events that contribute to the pathogenesis of SSc are still largely unknown. Inflammation and perturbation of the microvasculature seems to be the primary event which progressively stimulates the fibrotic process [7]. Malfunction of the endothelial and epithelial cells, lymphocyte differentiation, anti-endothelial auto-antibodies, oxidative stress and microchimerism are only some of the events that have been proposed as triggering vascular injury [8–11]. Immunological mediators, including cytokines, transforming growth factor-β, endothelin-1 and vascular endothelial growth factor are overproduced leading to accumulation of perivascular extracellular matrix and impairment of vascular morphology [12]. Consequent reduction in capillary density results in decreased blood flow and severe tissue hypoxia explaining the typical clinical manifestation of the disease such as Raynaud's phenomenon and ischemic digital ulcers. Apart from microvasculopathy, there is also increasing interest in large-vessel involvement and a possible higher risk for cardiovascular events in SSc patients, similar to what occurs in other systemic autoimmune disorders [13].

Nailfold videocapillaroscopy (NVC) is an established, validated diagnostic test for the assessment of the microcirculation, as well as the identification and the evaluation of microvascular angiopathy typically occurring in SSc [14–16]. NVC has a pivotal role in the prompt diagnosis of the disease, particularly in patients with Raynaud's phenomenon – the earliest and most common manifestation of the SSc [17,18]. Indeed NVC is included in the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) included the test in the update of the classification criteria for SSc [19]. NVC allows the evaluation of different components and specific morphologic changes of the microcirculation in SSc as well as the detection of defective neoangiogenesis and vasculogenesis. The relationship between clinical severity and NVC abnormalities has been documented to the point that NVC is currently considered a surrogate biomarker of SSc progression [20]. Several studies have investigated the association between NVC and severe manifestations of SSc, such as PAH, interstitial fibrosis, peripheral vascular disease and myocardial dysfunction, indicating particular NVC-detected abnormalities as potential predictors of future clinical complications [21–23].

The value of NVC in the diagnostic assessment, prediction of disease severity and evaluation of treatment efficacy in SSc patients with digital ulcers has been extensively reviewed in recent years [24]. This is beyond the scope of the present review, which focuses on visceral organ involvement. We present and discuss current data about the relationship between NVC findings and specific aspects of SSc particularly vascular and fibrotic complications, as well as the possible association between microvascular abnormalities with surrogate markers of macrovascular disease and autoimmune activation in SSc individuals.

2. Search strategy

A MedLine and Embase search was carried out according to published guidance on narrative reviews [25] using the following terms: systemic sclerosis, scleroderma, nailfold capillaroscopy, videocapillaroscopy, pulmonary hypertension, pulmonary arterial hypertension, interstitial lung disease, pulmonary fibrosis, myocardial fibrosis, atherosclerosis, scleroderma pattern. Original research papers and review articles focusing on a potential correlation between nailfold capillaroscopic findings and severe organ involvement in SSc registered until the end of January 2017 were selected to be included in this review. The records of recent rheumatological conferences were also searched for relevant abstracts. Publications not in English and data from ongoing research were excluded.

3. The 'scleroderma' pattern

A variety of structural abnormalities in the capillary bed can be recognized and be distinguished from a normal capillary pattern through NVC qualitative assessment. Such capillaroscopic changes can be demonstrated not only in SSc, but also in several connective tissue diseases, such as dermatomyositis, mixed connective tissue disease, systemic lupus erythematosus and Sjogren's syndrome [23]. Maricq et al. first systematized the specific capillaroscopic markers of SSc in comparison to normal [26]. A normal capillary pattern consists of homogeneously sized, perpendicularly oriented to the digital surface, parallel to each other, hairpin-shaped capillaries [27]. In contrast, capillaroscopic characteristics of microvascular damage include giant capillaries, microhemorrhages, loss of capillaries and decrease in capillary density, presence of avascular areas and angiogenesis [28]. These abnormalities are prevalent in >98% of SSc patients [29]. Many studies recognized two types of morphological aspects within the scleroderma pattern in patients with SSc: the 'active' and the 'slow' type [30]. Recently another classification for the vascular abnormalities was suggested in SSc proposed by Cutolo et al. [15]. According to this qualitative classification, three types of morphological NVC patterns are described: the 'early' pattern, characterized by few enlarged or giant capillaries and presence of microhemorrhages without evident loss of capillaries and relatively well-preserved capillary distribution; the 'active' pattern characterized by numerous giant capillaries, mild disturbance of capillary architecture and moderate capillary loss; and the 'late' pattern defined by severe capillary loss with extensive avascular areas, few or absent capillaries, disorganization of normal capillary area and ramified or bushy capillaries (Fig. 1). Morphological vascular patterns are correlated to the severity of SSc [15,21] as they seem to reflect the different phases of the disease, with the 'early' pattern characterizing the incipient vascular changes, and the 'active' and 'late' pattern representing the extensive capillary damage that characterizes the fibrotic phase of SSc [31]. Several studies have introduced qualitative and semi-quantitative grading models, assessing the number of vascular deletion areas or the number of detected capillary alterations per linear millimeter [32–34]. Recently, Sebastiani et al. also proposed a capillaroscopic skin ulcer risk index (CSURI) with specificity and sensitivity of 85.9% and 94.3%, respectively, to predict the onset of new digital ulcers [35]. However NVC remains an operator dependent examination and there is an emerging need for quantification of capillary alterations and re-evaluation of scoring systems in future well-designed studies aiming to minimize the subjectivity bias such scores may introduce.

4. Nailfold videocapillaroscopy and visceral organ involvement in SSc

4.1. NVC and PAH

PAH constitutes one of the most severe complications of SSc affecting dramatically both quality of life and survival. It occurs in approximately 10–15% of SSc patients [36,37]. Given that PAH and vasculopathy of digital arteries are considered two guises of SSc vascular disease with different topographic distribution across the microvasculature, the hypothesis that structural and morphological capillary