

A New Way of Thinking about Systemic Sclerosis: The Opportunity for a Very Early Diagnosis

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ABSTRACT: Systemic sclerosis (SSc) is a heterogeneous chronic autoimmune disease that it is extremely difficult to diagnose in the early phase, resulting in a critical delay in therapy which is often begun when internal organ involvement is already irreversible. The ACR or LeRoy criteria have a low sensitivity for the early phases; these criteria were replaced by the ACR/EULAR 2013 criteria which improved the disease classification. Therefore, the SSc diagnosis may be delayed for several years after the onset of Raynaud's phenomenon (RP) and even after the onset of the first non-RP symptom. RP, antinuclear antibodies (ANA) positivity, and puffy fingers were recently indicated as "red flags" (by the VEDOSS project) – that is, the main elements for suspicion of SSc in the very early phase of the disease. Confirming the diagnosis requires further tests, particularly nailfold videocapillaroscopy and evaluation of specific disease antibodies (anti-centromere and anti-topoisomerase I). In this way, the VEDOSS project identified patients in the very early phase of disease enabling a "window of opportunity" whereby the physician can act with effective drugs to block or at least slow the progression of the disease. The principal challenge in the fight against SSc is to detect valid predictors of disease evolution in order to treat patients in the early stage of disease. While waiting to find valid predictors, a close follow-up of the patients with the VEDOSS red flags is essential, as is a close collaboration between rheumatologists and general practitioners in order to identify all potential SSc patients as soon as possible.

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Systemic sclerosis (SSc) is characterized by widespread fibrosis of the skin and internal organs, small vessel vasculopathy, and immune dysregulation with production of autoantibodies [1,2]. SSc has a heterogeneous clinical and unpredictable course and a high mortality rate in some cases due to resistance to therapy [3]. For this reason, SSc is considered one of the greatest challenges in the management of rheumatic diseases.

Severe organ-based complications are frequently observed in SSc, such as renal crisis, sudden death, interstitial lung dis-

ease, pulmonary arterial hypertension, and digital ulceration. These complications are responsible for the high case-specific mortality rate [3,4] and have prompted efforts to prevent any delay in diagnosis.

Despite the many advances in our understanding of the pathogenic mechanisms, the "red flags" that raise the suspicion of very early disease were only recently identified. Usually SSc is easy to diagnose in the advanced phase when skin fibrosis is evident with vasculopathy and organ involvement, but diagnosing SSc remains very difficult in the early phase. Until now, the criteria used for the diagnosis of SSc were characterized by a low sensitivity to identify patients in the early stages. In particular, the American College of Rheumatology (ACR) classification criteria, developed in 1980, require the presence of skin sclerosis proximal to metacarpophalangeal or metatarsophalangeal joints as major criteria, or the presence of two of three secondary criteria (sclerodactyly, digital ulcers, or lung fibrosis) which, as known, are missing in the early stages [5,6]. Therefore, the SSc diagnosis may be delayed for several years after the onset of Raynaud's phenomenon (RP) and even after the onset of the first non-RP symptom. For this reason, until a few years ago, many very early SSc patients were not recognized and therefore not classified as having SSc. These patients were left in limbo, not treated, and the disease was able to continue its natural course. In order to overcome the limitations of the ACR criteria, numerous attempts have been made over the years to propose new criteria but with limited effectiveness.

In 1996, the term pre-scleroderma was coined to identify patients with RP plus digital ischemic changes and typical nailfold capillary changes or disease-specific circulating ANA [7]. Subsequently, LeRoy and Medsger [8] proposed the term limited SSc (lSSc) for cases presenting with RP and either a SSc-type nailfold capillary pattern or SSc-selective autoantibodies. The aim of LeRoy and Medsger [8] was to define criteria for the early diagnosis and classification of SSc in patients who did not satisfy the ACR criteria for SSc [5]. Therefore, they did not mention which other symptom/sign/laboratory/instrumental finding should be considered as an exclusion criterion for a diagnosis of lSSc. A common characteristic of all the criteria proposed is the distinction between limited cutaneous disease (in which the skin lesions do not extend beyond the elbows and knees but may involve the face) and diffuse cutaneous disease

(which affects the thighs, arms and trunk) [1]. This sub-setting is useful in clinical practice but does not help define or understand early SSc. Thus, the difficulty to reach an early diagnosis precludes early treatment which might block the disease evolution and avoid tissue damage.

In a large prospective study, Koenig et al. [9] found that RP patients with scleroderma autoantibodies and/or typical capillaroscopic abnormalities and without any other clinical manifestation were 60 times more likely to develop definite SSc according to ACR criteria than other RP patients. At follow-up, 79.5% of patients with autoantibodies and abnormal findings on nailfold capillaroscopy at baseline had developed a definite SSc. Autoantibodies and microvascular damage were considered independent predictive factors for the progression of RP to SSc.

In 2013, the new ACR/EULAR classification criteria were published. These included specific autoantibodies positivity, videocapillaroscopy alterations, the presence of RF, and puffy fingers. These criteria were based on a scoring system according to which a patient with a score > 9 is classified as having SSc [10]. This current classification system is therefore characterized by a high specificity but still cannot identify patients in the very early phases. This reality implies that the diagnosis and, consequently, the therapy are delayed until skin involvement and/or internal organ involvement is evident [11-13] and already irreversible [14]. In fact, there is increasing evidence that organ involvement is early and subclinical when the patient is still completely asymptomatic [12,13].

Valentini et al. [12] showed that the subclinical involvement in SSc is early, while clinical signs of organ involvement may appear later. In most of their patients studied, the presence of SSc-related internal organ involvement was found, including an inverted mitral E/A ratio (i.e., early cardiac involvement), a diffusing lung capacity for carbon monoxide < 80% of the predictive value (i.e., early lung interstitial/vascular involvement), and/or basal low esophageal sphincter pressure < 15 mmHg (i.e., early esophageal involvement) [12].

The fact that organ involvement may be present from the earliest stages of SSc corroborates the necessity for a *very early* or at least an *early* diagnosis of SSc to determine the therapy that might achieve disease remission. For this reason it is crucial to focus on the earliest signs of disease, to look for valid predictors of its evolution, and to conduct a close follow-up of patients in order to capture the slightest change in the clinical condition as soon as possible. In this regard it is essential to identify and define the difference between “early” and “very early” SSc, which will lay the ground for further breakthroughs from the standpoint of pathogenesis as well. Several attempts were previously made to define the early phase of SSc [15], and recently even the concept of very early SSc has been widely accepted and investigated [16]. RP, despite its lack of specificity, was proposed as a pivotal sign in an earlier attempt to define criteria for the diagnosis of “early” SSc [9] and was also con-

sidered as the main “sentinel” sign [17] for the identification of “very early SSc” [16]. Evidence from the EULAR Scleroderma Trial and Research group (EUSTAR) database indicates that the mean time between the onset of RP and the first non-RP symptom or sign in SSc is 4.8 years in limited cutaneous SSc and 1.9 years in diffuse cutaneous SSc [18]. This time gap between the onset of signs and the diagnosis, mainly based on dermal or internal organ fibrosis, should now be considered as the “window of opportunity” for SSc patients. Therefore, the aim for a very early or early diagnosis becomes the definitive goal of the rheumatologist, providing the opportunity for the potential prevention of disease evolution and organ damage. For this reason, EUSTAR has proposed the new preliminary criteria for the diagnosis of “very early” SSc that are currently under validation (VEDOSS project: www.eustar.org). RP, antinuclear antibodies positivity, and puffy swollen digits turning into sclerodactyly are the red flags to suspect SSc and thus to send the patient to a referral center. The diagnosis of “very early” SSc is confirmed when specific autoantibodies (anti-centromere and anti-topoisomerase-I antibodies) and/or a capillaroscopic SSc pattern (early, active, late) are found [16]. Preliminary results of the VEDOSS study confirm the relevance of the red flags identified by EUSTAR and highlight the importance of puffy fingers in the identification of patients with a predisposition to develop very early SSc.

In practice, when RP is identified a complete history and a general examination are mandatory for an accurate differential diagnosis. Together with RP and puffy fingers developing into sclerodactyly, other pathognomonic signs, like teleangiectasias, digital ulcers and pitting scars, may strongly suggest that the disease is already evolving to an “early” SSc with internal organ involvement (dysfunctional lower esophageal sphincter, ground glass on high resolution chest tomography, diffusion lung capacity for carbon monoxide reduction on pulmonary function tests, and E/A ratio reversal). Any suspicion of SSc evolution to organ involvement may be easily confirmed or refuted by further specific investigations of internal organs involvement.

It is well known that RP is a common initial sign in many connective tissue diseases and, moreover, in SSc it may precede the onset of cutaneous or visceral sclerosis, in some cases even by decades (in particular limited SSc). Today, despite the usefulness of criteria to define very early SSc, the management of these patients remains a major challenge. In fact, the choice of an aggressive treatment, though logical and reasonable, still remains an option which may expose some patients to overtreatment and risks connected to side effects. The reality therefore is that the present criteria for *very early* SSc are not yet validated while the predictors of severity in this cohort of *very early* SSc patients have yet to be identified. These weaknesses obviously impair the capacity of the rheumatologist to act in due time. In practice, this evidence dictates the need for a stringent follow-up of patients to promptly identify the many

changing faces of SSc characterized by the heterogenous mix of vascular, skin and internal organ involvement.

Clearly, the ability to decipher the riddle of very early/early SSc and the capacity to provide new predictors of severity are crucial issues today. Once these are clarified we may hopefully look ahead to the window of opportunity as a unique chance to design a treatment for SSc before damage is done. For the moment, the only feasible clinical strategy in *very early* SSc remains a rigorous follow-up program to foster the real-time detection of early internal organ involvement followed by an aggressive therapeutic agenda. The EUSTAR effort to validate the criteria with the VEDOSS project will definitively open a new avenue in SSc, shedding light on a gray zone today represented by the *very early/early* phase of the disease.

CONCLUSIONS

The new ACR/EULAR criteria have significantly improved the capacity of rheumatologists to classify SSc and thus detect patients earlier in the disease. While these criteria are useful, sensitive and specific, a percentage of patients remain unclassified. The VEDOSS criteria can identify the largest percentage of patients who already have SSc in the very early phase before they reach the criteria for classification. The concepts of VEDOSS and early SSc are now evolving rapidly and the new VEDOSS criteria will be validated to empower the identification of SSc patients in the earliest phase possible. The VEDOSS concept could well be a new way to approach SSc. Today rheumatologists may diagnose SSc either very early or in the early phase of the disease, allowing them to institute treatment promptly. But we are still lacking predictors of evolution and severity. This means that clinicians have difficulty identifying those patients who will progress and those who will not. For the present, the red flags remain a valid and crucial tool to track patients in the earliest phase of the disease and at risk of progressing to overt disease; with the window of opportunity an appropriate treatment can be begun before organ damage becomes irreversible. Further studies are needed to identify valid predictors of disease evolution to avoid overtreatment of patients at an early stage of disease.

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“The most potent weapon in the hands of the oppressor is the mind of the oppressed”

Steve Biko (1946-1977), South African anti-apartheid activist in the 1960s and 1970s. A student leader, he later founded the Black Consciousness Movement which would empower and mobilize much of the urban black population. He died in police custody. Although never a member of the African National Congress (ANC), he was included in their pantheon of struggle heroes. Nelson Mandela said of Biko: "They had to kill him to prolong the life of apartheid"

“Pleasure in the job puts perfection in the work”

Aristotle (384–322 BC), Greek philosopher and scientist