# EARLY SCLERODERMA

## RANA SKLERODERMA

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## Abstract

Systemic sclerosis (SSc) is a chronic autoimmune disease, characterized by a high level of clinical heterogeneity and associated with a high morbidity along with the highest disease-specific mortality of all autoimmune connective tissue diseases. SSc is quite easy to diagnose in the advanced phase, i.e., when it has already evolved to obliterative vasculopathy and skin and internal organ fibrosis, but it is difficult to establish a diagnosis in the early phase. This limits the possibility to start early treatment, as well as the potential for prevention of disease evolution and tissue damage. Raynaud's phenomenon (RP) has been proposed as one of the defining clinical features for the diagnosis of "early" SSc, so that particular attention should be paid to this symptom, even in the absence of other signs of the disease. Based on previous diagnostic criteria, the diagnosis of SSc can be delayed for several years after the onset of RP, and even after the onset of the first non-RP symptom.

This time gap between symptoms and diagnosis, mainly based on dermal or internal organ fibrosis, is a "window of opportunity" that could represent a chance to intervene earlier in the disease course, thus potentially preventing organ damage.

The definition of Very early SSc has been proposed as a state characterized by RP, puffy fingers, disease-specific autoantibodies, and pathognomonic microvascular alterations at capillaroscopy, without skin and internal organ involvement. In patients with the above symptoms further investigations such as esophageal manometry, B-mode echocardiography, and lung function tests are recommended to detect preclinical alterations of internal organs in SSc. Recently, new classification criteria have been proposed with the goal to identify patients in the earliest phase of the disease. However, as predictors of the future course of the disease are still unknown, patients must be followed up regularly, even though the ideal frequency of visits has not yet been established.

**Keywords:** systemic sclerosis, early diagnosis, treatment, classification criteria, early systemic sclerosis

## Sažetak

Sustavna skleroza (SSc) kronična je autoimuna bolest obilježena visokim stupnjem heterogenosti i povezana s visokim morbiditetom, kao i s najvišim mortalitetom specifičnim za samu bolest, u odnosu na sve druge autoimune bolesti vezivnog tkiva. SSc moguće je jednostavno dijagnosticirati u uznapredovaloj fazi, dakle kad se već razvila obliterativna vaskulopatija te fibroza kože i unutrašnjih organa, ali teško je postaviti dijagnozu u ranoj fazi bolesti. Ta činjenica ograničuje mogućnost ranog liječenja i potencijalnog preveniranja razvoja bolesti i oštećenja tkiva. Raynaudov fenomen (engl. skr. RP) predložen je kao jedno od definirajućih kliničkih obilježja za dijagnozu „rane" SSc te stoga pozornost valja poglavito usmjeriti na taj simptom, čak i u slučaju odsustva drugih znakova bolesti. Na temelju prethodnih dijagnostičkih kriterija dijagnoza SSc može biti postavljena nakon više godina od početka RP, pa i nakon pojave prvih simptoma nevezanih za RP.

Ovaj je vremenski raskorak između pojave simptoma i postavljanja dijagnoze, ponajprije temeljen na fibrozi kože i unutrašnjih organa, „prozor mogućnosti" koji bi mogao biti vrijeme za intervenciju u ranoj fazi bolesti te time potencijalno prevenirati oštećenje organa.

Prijedlog definicije vrlo rane SSc jest stanje obilježeno RP-om, difuznom oteklinom prstiju, pozitivnim protutijelima specifičnima za bolest i patognomoničnim mirkovaskularnim promjenama vidljivima na kapilaroskopiji, a bez zahvaćenosti kože i unutrašnjih organa. U bolesnika s navedenim simptomima, radi otkrivanja pretkliničkih promjena na unutarašnjim organima u SSc, mogu se provesti i pretrage kao što su ezofagealna manometrija, ehokardiografija u B-modu i funkcijski testovi pluća.

Nedavno su predloženi novi klasifikacijski kriteriji radi identificiranja bolesnika u najranijoj fazi bolesti. Međutim, prediktori tijeka bolesti i dalje su nepoznati te je stoga potrebno redovito praćenje, iako idealna učestalost kontrolnih pregleda nije utvrđena.

**Ključne riječi:** sustavna skleroza, rana dijagnoza, liječenje, klasifikacijski kriteriji, rana sustavna skleroza

Systemic sclerosis (SSc) is a chronic disease, characterized by fibrosis of the skin and internal organs, small-vessel vasculopathy, and immune abnormalities with autoantibody production. It was defined as "one of the most terrible of all human ills" and a "shrinking skin of steel" by William Osler in 1898, highlighting the devastating complications affecting SSc patients. It is a heterogeneous disease associated with a high morbidity and with the highest disease-specific mortality of all autoimmune connective tissue diseases (1, 2). In several studies, the incidence of SSc is reported to be between 4 and 20 new cases per 1,000,000, with a prevalence ranging between 30 and 450 cases per 1,000, 000 (3-5). Moreover, the patient's appearance changes owing to skin sclerosis, muscle atrophy, and joint contracture; consequently, SSc also has a substantial impact on the patient's emotional and psychological well-being (6, 7), resulting in loss of function, impairment of quality of life, and a high socio-economic cost. This unpredictable disease still represents a great challenge for the rheumatologist because, despite the many advances made in the understanding of the pathogenetic pathways and the development of new targeted therapies, early diagnosis remains the weak point, although it is the crucial element in the management of SSc patients (8). Thus, it is fundamental to focus on the earliest signs of the disease, to look for valid predictors of its evolution, and to perform a close follow up of patients in order to capture the slightest change in the clinical condition as soon as possible. Population-based studies showed that mild SSc is a more frequent disease than has previously been suspected (9).

In fact, SSc is quite easy to diagnose in the advanced phase, when characterized by an obliterative vasculopathy and skin and internal organ fibrosis, but diagnosis can be difficult in the early phases. The current classification criteria used for the diagnosis, the American College of Rheumatology (ACR) or LeRoy and Medsger criteria (10, 11), which allow only for the identification of patients with skin thickness, are thus not sensitive to early diagnosis of SSc when this feature is usually missing. This suggests that the diagnosis and, consequently, appropriate treatment are delayed until skin involvement and/or internal organ involvement are evident (12-14), and the damage is probably already irreversible (9).

Raynaud's phenomenon (RP) is the most common initial symptom in many connective tissue diseases (CTDs), and particularly in SSc (15, 16). Despite its poor specificity, it has been proposed as one of the defining clinical features for the diagnosis of "early" SSc (10). In fact, it is considered as the main sentinel sign to identify patients at higher risk of developing SSc. Thus great attention is devoted to the identification of its true diagnostic value, particularly in combination with other typical early features of SSc. In a large prospective study, Koenig et al. showed that RP patients with SSc marker autoantibodies and/or typical capillaroscopic abnormalities but without any other clinical manifestations, are 60 times more likely to develop definite SSc (by ACR preliminary criteria) than other RP patients (17). RP may sometimes precede the onset of cutaneous or visceral sclerosis by decades (especially in its limited form), and for this reason particular attention should be paid to this symptom even in the absence of other signs of the disease. Nevertheless, based on previous diagnostic criteria, the diagnosis of SSc can be delayed for several years after the onset of RP, and even after the onset of the first non-RP symptom.

Preliminary data from the EULAR Scleroderma Trial and Research group (EUSTAR) data indicate that the time gap between the onset of RP and the first non-RP symptom or sign in SSc is a mean of 4.8 years in limited cutaneous SSc (lcSSc) and 1.9 years in diffuse cutaneous SSc (dcSSc) (14). The delay between symptoms and diagnosis, mainly based on dermal or internal organ fibrosis, could be considered as a "window of opportunity" for these patients, allowing rheumatologists to intervene earlier in the disease course, thus potentially preventing organ damage.

To decrease the diagnostic delay, the identification of other earliest signs and symptoms of the disease are considered fundamental in the clinical practice. Today the variety of SSc diagnostic and classification criteria at our disposal enables us to identify SSc patients as early as possible, in order to block or slow the disease progression and reach an early monitor of organ-based complications.

In the past, SSc was classified and diagnosed according to the ACR classification criteria (1980), which required either the presence of skin sclerosis proximal to the MCP or MTP joints, or the presence of two of three secondary criteria (sclerodactyly, digital ulcers, or lung fibrosis) (18). To overcome the limitations of these ACR criteria, many classification schemes have been developed, but all of them distinguish between limited cutaneous SSc (the skin lesions are distal to the elbows and knees +/- the face) and diffuse cutaneous SSc (the skin involvement is proximal to the elbows and knees, often including the trunk +/- face) (10, 11).

In 2001, Le Roy and Medsger proposed criteria for the diagnosis and classification of "early" SSc, including RP with SSc-type nailfold capillary pattern (giant capillaries and/or avascular areas) and/or SSc specific autoantibodies (10). Three years later, Medsger TA jr identified early SSc as a disease stage that precedes the development of atrophic lesions and irreversible vascular occlusion in dSSc (<3 years from the first non-RP symptom) or lSSc (<5 years) (17). In 2008, early SSc patients with a high probability of developing SSc during a long-term follow up were considered those with RP and SSc-specific autoantibodies, or typical capillaroscopic abnormalities, or both (17).

The new criteria proposed by EUSTAR (European League Against Rheumatism Scleroderma Trial and Research Group) represent a turning point in the approach to the diagnosis of SSc. According to these criteria, a very early diagnosis of SSc (VEDOSS) is suspected in the presence of the three red flags (RP, PF, and antinuclear antibody (ANA) positivity), and also if disease-specific autoantibodies (anticentromere Ab (ACA) or anti-topo I Ab (Scl70)) or microvascular alterations are detected by nailfold videocapillaroscopy. If all of the above are present, the final diagnosis of VEDOSS is made. These criteria have been selected by a wide Delphi technique among experts on systemic sclerosis (18). Besides, it was shown that PF is a fundamental clinical criterion of the very early phase (20), and for this reason PF was also included in the recently revised ACR/EULAR classification criteria for SSc (20).

If a patient fulfills the VEDOSS criteria, further investigations to assess internal organ involvement are mandatory. In particular, esophageal manometry, B-mode

echocardiography, lung function tests, and esophageal manometry are recommended to detect preclinical alterations of internal organs in SSc.

More recently, an international ACR/EULAR collaborative initiative developed new classification criteria for SSc. Seven new items (including RP, puffy fingers, fingertip lesions, telangectasias, abnormal nailfold capillaries, SSc-related autoantibodies, pulmonary arterial hypertension, and/or lung disease) were identified and weighted, and a provisional threshold was proposed (20). A total score of 9 or more allows to classify a patient as affected by systemic sclerosis. The presence of skin thickening of the fingers of both hands extending proximal to the MCP joints is a sufficient criterion to reach 9 points. The higher sensitivity of these new classification criteria in respect to the previous ACR criteria has been recently reported with the analysis of a cohort of 304 patients with early or established SSc, demonstrating that they classified more patients as definite SSc patients than the previous ACR criteria (21, 22).

To highlight the importance of early diagnosis, Valentini et al. have shown that the internal organ involvement in SSc is early and subclinical, and could also be present in patients without skin involvement (23). In a high proportion of patients studied they reported early cardiac involvement with an inverted mitral E/A ratio, early lung involvement with a reduction of transfer factor for carbon monoxide (TLCO) less than 80% of the predictive value, and/or a basal lower esophageal sphincter pressure of <15mmHg (i.e., early esophageal involvement). These data could identify a subset of SSc patients who have already evolved to an early organ involvement and therefore might be identified as early rather than very early SSc. Interestingly, Lepri et

al. found that in the very early phase an esophageal and anorectal involvement could also be present in SSc patients (24). Additionally, digital ulcers, a common vascular complication in SSc, seem to be a sentinel sign for early internal organ involvement in very early systemic sclerosis. Since DUs represent a high socio-economic cost, the early detection of patients with a high risk of developing DUs could allow a preventive treatment, with a reduction of morbidity and social costs (25).

More recently, Valentini et al. have considered early SSc as a disease stage in which classification criteria are not yet satisfied, and there are different degrees of probability to develop the full-blown disease ranging from low to very high, but without absolute certainty (26).

However, when a very early SSc diagnosis is made, there are two possibilities: first, the patient does not fulfill the ACR/EULAR criteria for SSc and should be followed up closely and evaluated before a treatment is chosen; second, the patient already fulfills the ACR/EULAR criteria for SSc and further investigations show an internal organ involvement, thus classifying the patient as early SSc.

In conclusion, today an early diagnosis of SSc and a definite SSc classification are mandatory to achieve an early window of opportunity in order to decide whether an aggressive treatment is necessary (27). As reliable predictors of the future course of the disease are still unknown, the patients must be followed up regularly, even though the ideal frequency of visits has not yet been established. Further studies are required to identify predictors of evolution that will allow us to understand which patients will evolve to an established disease with visceral involvement, in order to treat them promptly before internal organ damage occurs (28).

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