

Systemic sclerosis sine scleroderma

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Abstract

Systemic sclerosis is a rare generalized disease with scleroderma, i.e. skin thickening as one of the most common symptoms. The disease has 2 main subsets, diffuse and limited forms. The subset known as systemic sclerosis sine scleroderma (ssSSc) is a very rare subset characterized by the total or partial absence of cutaneous manifestations of systemic sclerosis with the occurrence of internal organ involvement and serologic abnormalities. The classification of ssSSc into 3 groups was proposed. Type I (complete) is characterized by the lack of any cutaneous changes typical for the disease at least until systemic sclerosis-related insufficiency of any internal organ occurs. Type II (incomplete) is characterized by the absence of sclerodactyly, but other cutaneous involvements (e.g. calcifications, telangiectasies, pitting scars) can be found. Type III (delayed) is characterized by clinical internal organ involvement typical for systemic sclerosis that has appeared before skin changes (complete or incomplete). In general, the demographic and clinical characteristics of the ssSSc patients suggest that they are similar to those with diffuse or limited form of the disease. Diagnosis of ssSSc still remains difficult and this disease form should be considered in all cases of unexplained fibrotic involvement of the internal organs.

Key words: systemic sclerosis, scleroderma, sclerodactyly, internal organ fibrosis

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Systemic sclerosis is a rare generalized connective disorder of unknown etiology and unclear pathogenesis. It is generally accepted that the disease is characterized by widespread fibrosis of the skin and internal organs, vascular abnormalities and immune disturbances. On the other hand, systemic sclerosis is considered as a heterogeneous disorder (scleroderma spectrum disorders) and has a broad spectrum of clinical features.¹ The main subsets of systemic sclerosis are limited cutaneous form and diffuse form. There are several differences between the subsets, including the most important, which is that internal organ involvement is significantly delayed and relatively minor in patients with limited cutaneous form of systemic sclerosis. Other differences include different distributions of cutaneous changes and the common occurrence of different autoantibodies (against topoisomerase I, Scl-70 in patients with diffuse form and antinuclear antibodies, ACA in those with limited form).^{2,3}

Skin involvement is considered a cardinal feature of systemic sclerosis, and the name “scleroderma” means hardening of the skin. Cutaneous manifestations are also crucial in the initial diagnosis. Although the disease is a heterogeneous disorder, skin involvement usually develops at the early stage of the disease and is preceded by Raynaud’s phenomenon. Skin changes begin with non-pitting edema that is followed by the thickening of the skin leading to sclerodactyly. Tapering of fingertips and digital ulcers are common features seen in patients and they result from ischemia due to vasculopathy. Vascular insufficiency may cause atrophy and auto-amputation of the distal parts of the fingers. Cutaneous manifestations include typical facial features, teleangiectasias, abnormal calcium depositions in the subcutaneous tissue, altered pigmentation (“salt and pepper skin”), loss of hair follicles and sebaceous glands with resultant dryness.⁴ Skin alterations may be localized in different parts of the body. A small number of the patients with systemic sclerosis suffer from systemic sclerosis sine scleroderma (ssSSc), a disease subset characterized by the presence of visceral involvement occurring in the absence of skin manifestations. The subset, sometimes called “visceral scleroderma”, was described for the first time in detail by Rodnan and Fennel in 1962, who also coined the term “progressive systemic sclerosis sine scleroderma”.⁵ The only earlier case was reported by Abrams et al.⁶ They published in 1954 a description of a patient with visceral scleroderma, but without detectable skin involvement. ssSSc is a rare form of the disease and its real prevalence is difficult to estimate. It is believed that some ssSSc cases remain underdiagnosed and are considered to be various forms of idiopathic fibrosis of internal organs. In 2013, joint groups of the American College of Rheumatology and European League Against Rheumatism elaborated new classification criteria for systemic sclerosis.⁷ Three major hallmarks of systemic sclerosis were included in the list of criteria: skin and organ fibrosis, signs of vas-

culopathy, and autoantibodies. Internal organ involvement is included in the criteria as the interstitial lung disease resulted from the pulmonary fibrosis. A sufficient criterion is skin thickening of the fingers of both hands extending proximal to the metacarpophalangeal joints. The point scoring system is applied in the classification criteria, and individuals with a score ≥ 9 are classified as having systemic sclerosis. According to the criteria, score 9 can be achieved in a patient without skin thickening when systemic sclerosis-related autoantibodies, Raynaud’s phenomenon, interstitial lung disease or pulmonary arterial hypertension and abnormal nail fold capillaries are detected. On the other hand, it is clearly stated that the criteria are designed for the inclusion of patients in studies and are not diagnostic criteria per se. Diagnosis of systemic sclerosis can be based on other symptoms and signs, including those related to internal organ involvement, and only a part of the patients classified as having systemic sclerosis are being diagnosed as having the disease. This is of importance, especially in patients with ssSSc.

Prevalence

Limited epidemiological data on ssSSc is available. Marangoni et al. retrospectively analyzed 947 consecutive patients with systemic sclerosis treated in two academic medical centers in Brazil.⁸ They were able to identify a very high rate of the ssSSc patients, i.e. 79 cases (8.3%). Poormoghim et al. compared patients with limited cutaneous systemic sclerosis and ssSSc, who were evaluated at the University of Pittsburgh Division of Rheumatology during 24 years (1972–1996), and they were able to identify 48 cases of ssSSc and 507 patients with limited cutaneous systemic sclerosis, 9 and 91%, respectively.⁹ It can be roughly estimated that ssSSc patients account for about 5% of all patients with systemic sclerosis (this calculation was based on the rate of patients with diffuse subset, i.e. 40% of all ones with systemic sclerosis). The low rate of ssSSc subset was reported in the German and Spanish nationwide registry analyses, i.e. 1.5 and 7.5%, respectively.^{8,10} Most of the literature is limited to descriptions of isolated cases, usually containing additional rare features, complications or associated conditions. According to Marangoni et al., the total number of 139 cases was reported until 2012.⁸ In 2014, Diab et al. analyzed data from 1,417 subjects with systemic sclerosis in the Canadian Scleroderma Research Group registry.¹¹ Twenty-seven subjects (1.9%) were considered as ssSSc with a mean follow-up of 2.4 years. The initial diagnosis that had been made at the first visit was more common, and had been set in 57 subjects (4.0%), but more than a half of them were reclassified as limited systemic sclerosis within 1.9 years. Moreover, the ssSSc patients had no sclerodactyly (as per definition) but had some

other cutaneous involvements typical for systemic sclerosis (e.g. calcinosis 15.4%, telangiectasias 69.2%, digital pits 11.1%). Additionally, nail fold capillary abnormalities were detected in 74.1% of ssSSc patients. Thus, the ssSSc subgroup was not without any cutaneous involvement.

Definition and classification

It is important to specify the term “ssSSc” because it is used in medical literature to describe patients with at least 2 variants systemic sclerosis. The 1st variant described as ssSSc consists of patients who have no cutaneous involvement during the whole period of clinical observation but suffer from sclerodermatous internal organ involvement. The remaining variant also termed ssSSc consists of patients who suffer from visceral manifestation typical for systemic sclerosis that was diagnosed when they had no cutaneous manifestation but later characteristic skin features are visible.

The problem of skin manifestation should also be specified. Some reports considered patients with visceral involvement and some cutaneous manifestations (e.g. telangiectasias) but without skin thickening (i.e. “true” scleroderma) as those belonging to ssSSc subset, while other reports consider ssSSc patients only when they have no cutaneous features typical for systemic sclerosis. All these discrepancies, together with the scarce data on ssSSc in the literature, are the main difficulty for a comprehensive analysis of the problem.

In this paper, we propose a detailed classification of ssSSc based on 2 features. The 1st feature is the lack of sclerodactyly in patients with evidence of sclerodermatous internal organ involvement detectable during the whole period of clinically overt disease, at least until any internal organ insufficiency related to systemic sclerosis occurs. Despite the lack of sclerodactyly, the patients can have other cutaneous involvements typical for systemic sclerosis (e.g. telangiectasias). The absence of any sclerodermatous skin involvement is a basis for classifying those patients as “complete” (type I), while the lack of thickening coexisting with other typical cutaneous features is named “incomplete”. The 2nd feature included in the classification is a sequence of skin and internal organ manifestations. We propose type III of ssSSc comprising patients with “delayed cutaneous involvement”, i.e. those whose cutaneous involvement becomes detectable later than clinically overt internal organ manifestations. Patients with type III of ssSSc may suffer from a “complete” or an “incomplete” form of the disease as well. Based on these factors, the following classification of patients with ssSSc is proposed:

ssSSc type I: complete visceral scleroderma – patients with evidence of sclerodermatous involvement of an internal organ or organs and without any sign or symptom of skin involvement typical for systemic sclerosis.

The Raynaud’s phenomenon as a vascular abnormality can be presented. There is no skin involvement at least until systemic sclerosis-related insufficiency of any internal organ is detectable.

ssSSc type II: incomplete visceral scleroderma – patients with evidence of sclerodermatous internal organ involvement with cutaneous manifestations typical for systemic sclerosis other than skin thickening, i.e. without sclerodactyly.

ssSSc type III: with delayed cutaneous involvement – patients with evidence of internal organ involvement typical for the disease and no sign of cutaneous sclerodermatous involvement, at least when internal organ manifestation becomes overt (complete form), or no skin thickening signs, at least when internal organ manifestation becomes overt (in complete form).

In most cases of ssSSc with delayed cutaneous involvement, the clinical picture of the disease is indistinguishable from diffuse systemic sclerosis. Analysis of the sequence of appearance of the disease manifestations is the only way to distinguish this type of ssSSc from diffuse systemic sclerosis with early development of skin involvement.

A distinction of the above-described types of ssSSc is based on the stage of the disease, when internal organ and cutaneous abnormalities become overt. Due to the variability of internal organ involvement, it is difficult to establish the exact necessary period of observation. The proposed classification is based on detectable (and to some extent measurable) organ insufficiency. Practically, all internal organ involvement has well-known criteria for organ insufficiency or failure. The time point is proposed to establish the period defining the lack of skin abnormalities before the appearance of at least 1st stage of organ insufficiency. The term “complete” or “incomplete” was introduced to separate cases of ssSSc without any sclerodermatous cutaneous manifestations from those with some involvement of the skin but without evidence of thickening. Raynaud’s phenomenon that is primarily vascular abnormality is not considered as a skin abnormality.

Analysis of almost 1,500 patients revealed that female to male ratio in ssSSc patients is about 9 : 1 and is rather similar to the total group of systemic sclerosis patients. Forty per cent of the ssSSc patients had autoantibodies against topoisomerase I (55% in diffuse form of the disease) while 35% had anticentromeric antibodies (62% in those with localized form of systemic sclerosis). This suggests that, at least immunologically, ssSSc cannot be considered as a subset of any “major” form of the disease. Almost all internal organ involvements were found to be more common in ssSSc patients as compared with the total group and this is related to the role of visceral fibrosis in the diagnosis of ssSSc. There was no difference between patients with ssSSc and all the patients with systemic sclerosis at the age of the onset of Raynaud’s phenomenon or at the age of organ involvement.¹⁰

Clinical picture

The study conducted by Diab et al. is the largest reported cohort of ssSSc patients and is a very valuable tool for comparing those patients with the ones with diffuse systemic sclerosis and limited systemic sclerosis.¹¹ Baseline demographic and clinical characteristics of subjects with diffuse, limited and ssSSc disease were found to be similar. They included the proportion of women to men, duration of overt disease and age at disease onset. Clinical signs and symptoms reflecting the involvement of a few internal organs were less prevalent in ssSSc than in diffused or limited subsets of the disease, including esophageal dysmotility, inflammatory polyarthrititis, myositis and other than esophageal gastrointestinal symptoms. Intestinal lung disease was as common in ssSSc patients as in those with limited systemic sclerosis, and was detected in about 1/4 of the patients. This was reported earlier by Fischer et al.¹³ Also, pulmonary hypertension was present in about 11% of the patients with ssSSc, similarly to other subgroups of systemic sclerosis patients.

The slightly lower prevalence of internal organ involvement at the baseline characteristics of the study is an indication of high awareness of ssSSc in the Canadian Scleroderma Research Group registry. In most of the cases reported in the literature, only severe internal organ manifestations attracted the attention of physicians because of the possibility of diagnosing ssSSc

The study conducted by Diab et al. once again confirmed that ssSSc is a rare form of the disease, especially in the rare cases without any skin involvement typical for systemic sclerosis.¹¹ The general profile of ssSSc patients is similar to the others, especially those suffering from limited systemic sclerosis. The lack or atypical picture of cutaneous manifestations is the key differential feature.

The clinical picture of ssSSc is similar, and gastrointestinal and pulmonal manifestations are the most common in these patients. The involvement of respiratory and alimentary systems seems to be relatively highly symptomatic and detectable, and this finding may explain their common occurrence both in reported series of the patients and in the majority of individual case reports. Poormaghim et al. found in ssSSc patients gastrointestinal involvement in 79% (31/39), pulmonary in 68% (32/47) and cardiac in 9% (4/45) only.⁹ The large group of ssSSc patients reported by Marangoni et al. confirmed that esophageal involvement was the most frequent visceral manifestation (83%) and was followed by pulmonary involvement (68%).⁸ Similar findings were described in the German and Spanish groups of ssSSc patients.^{8,10} Esophageal dysmotility was shown in 73% and 45% of the patients, while interstitial lung disease was found in 73% and 64%, respectively. Gastrointestinal manifestations include swallowing disturbances, crampy abdominal pain, nausea or vomiting. Gastro-

esophageal reflux disease is a frequent diagnosis in systemic sclerosis patients of all subsets, including those with ssSSc. Pulmonary involvement symptoms include predominant dyspnea at early stages of exertion. Interstitial lung disease and pulmonary hypertension are the most common pulmonary manifestations.

Toya and Tzelepis carried out an analysis of cardiopulmonary involvement in 108 cases of ssSSc described in the literature.¹² Cardiac involvement was documented in 25% of the patients. The most common manifestations were chronic heart failure, pericardial effusions, conduction disturbances or arrhythmias. It is suggested that myocardial fibrosis is the underlying cause of cardiac manifestations.

Diab et al. suggested that the prevalence of myositis in patients with ssSSc is lower than in those with other subsets of the disease.¹¹ This was confirmed by Sánchez-Montalya et al., despite a rather common occurrence of anti-SSA/Ro52 autoantibodies in patients with ssSSc.¹⁴ In 132 consecutive patients with SSc and anti-SSA/Ro52 autoantibodies patients with ssSSc constituted 22.7%. It is also suggested that acute phase reactants are more commonly elevated in patients with ssSSc than in other subsets.¹⁰

Renal involvement

There are discrepancies in the estimation of frequency of renal involvement in patients with ssSSc. Poormoghim et al. showed that the kidneys are uncommonly involved in the patients and this finding supported the suggestion that ssSSc patients are at least similar or even constitute a subgroup of patients with limited cutaneous systemic sclerosis.⁹ On the other hand, Hunzelmann et al. reported that renal involvement is twice as common in patients with ssSSc than it is in patients with systemic sclerosis.¹⁰ Additionally, renal insufficiency was also more than twice as common in the patients as compared to the total group of systemic sclerosis patients. An analysis of the literature revealed a relatively high rate of case reports describing patients with renal failure due to systemic sclerosis with or without delayed cutaneous manifestations.¹⁵⁻¹⁸

Renal involvement in ssSSc patients manifests in 2 different forms: scleroderma renal crisis and chronic forms leading to renal failure. Scleroderma renal crisis is characterized by the acute onset of severe hypertension, acute left ventricular failure and retention of nitrogen bodies due to rapid progressive renal failure. Few patients with renal crisis due to systemic sclerosis but without skin involvement at the onset of the crisis were reported.¹⁵⁻¹⁸ In most of the cases, rapid development of skin changes typical for the disease occurred after renal failure. Less common is the slow development of renal failure. Chung et al. reported nephritic syndrome in women with ssSSc akin to those seen in patients with other forms of systemic sclerosis.¹⁹

Prognosis

Retrospective analysis of internal organ involvement in ssSSc patients is limited, due to variety of criteria used in investigations. Some studies were based on clinically overt symptoms, while others applied more and less sensitive laboratory or imagine methods. It is well known that the evaluation of the cardiopulmonary and gastrointestinal systems in patients with systemic sclerosis with functional or imagine test revealed a higher rate of involvement than the analysis of clinically overt symptoms. The same applies to ssSSc patients. This is probably the source of discrepancies between published series and individual reported cases.

Special situations

A search of literature revealed some descriptions of an atypical course of ssSSc. It is impossible to conclude from these anecdotal reports, but due to the rarity of the disease at least a few of them should be mentioned.

A case of ssSSc with multiple intracerebral hemorrhages and significantly high antitopoisomerase-I autoantibodies is akin to an earlier description of limited systemic sclerosis and vasculitis overlap syndrome.^{20,21} Recently, Anand et al. reported a case of ssSSc with overlap syndrome and characterized by ANCA associated vasculitis.²² The main clinical abnormality was pulmonary fibrosis. A case of ssSSc with anterior uveitis has also been recently reported.²³

Scleroderma-like disease exposed to epoxy resin polymerization was also reported in a form of ssSSc.²⁴ It is an absolutely unique case of such a form of the disease.

Concluding remarks

Diagnosis of ssSSc is difficult. From a practical point of view, it is important to consider the diagnosis of ssSSc in patients with multisystemic internal organ abnormalities that cannot be attributed to other diseases. The occurrence of Raynaud's phenomenon or antibodies typical for systemic sclerosis is useful for establishing a diagnosis. Vascular abnormalities detectable with capillaroscopy are included in the new classification criteria. Capillaroscopic evaluation is a valuable tool in the diagnostics of ssSSc.²³

Systemic sclerosis is still a very enigmatic disease. Pathomechanism of fibrosis and its localization remains unknown. The elucidation of this phenomenon may be a key to understand the sequence and grade of skin and internal organ involvement. The current classification and distinction of ssSSc as a separate subset is based exclusively on clinical symptomatology and the course of the disease.^{25,26} Unfortunately, a diagnosis of ssSSc has

no substantial effect on the management of the patients and the general rules of organ-oriented therapy are to be applied in those patients.

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