Very early diagnosis of systemic sclerosis

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KEY WORDS

ABSTRACT

Systemic sclerosis (SSc) is an incurable chronic autoimmune disease associated with high morbidity and mortality. The current validated or proposed criteria are not appropriate to make a very early diagnosis of SSc. This implies that the diagnosis of SSc and, consequently, an appropriate therapy are delayed until the appearance of skin involvement and/or clinically detectable internal organ involvement when microvascular remodeling, tissue fibrosis, or atrophy are already irreversible.

In a recent Delphi exercise, 4 signs/symptoms have been identified as necessary for the very early diagnosis of SSc: Raynaud's phenomenon (RP), puffy swollen digits turning into sclerodactily, antinuclear antibodies and specific SSc antibodies (anticentromere and antitopoisomerase-I antibodies), and abnormal capillaroscopy with scleroderma pattern.

Patients with very early SSc are the target of the recently launched the VEDOSS program, which has been designed to diagnose SSc very early and to examine whether this may change the disease prognosis. Although patients with RP, autoantibodies, and SSc capillaroscopic pattern could be easily followed up, there is still no agreement on the predictors that may allow us to identify patients who will develop an established disease.

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Introduction Systemic sclerosis (SSc) is a chronic disease characterized by widespread fibrosis of the skin and internal organs, a small-vessel vasculopathy, and evidence of immune dysregulation with the production of autoantibodies. The incidence of SSc is estimated between 4 and 20 new cases per 1,000,000 per year and the prevalence between 30 and 450 cases per 1,000,000.[1,2] In the United States, it ranges across studies from 3 to 21/10[6] population.[3] It is a clinically heterogeneous disease ranging from a milder form with less extensive involvement of the internal organs to a more rapid widespread internal organ involvement resulting in disability and death within several years.[4]

All classifications distinguish between limited cutaneous SSc, in which the skin lesions do not extend beyond the elbows and knees and involve the face, and diffuse cutaneous SSc, which affects also the thighs, arms, and torso. The current division of SSc into subsets is useful in the clinic but cannot help define or understand very early SSc.

In fact, the preliminary criteria developed since 1980 by the American College of Rheumatology

(ACR) are ill-suited to early disease and limited subsets with no skin lesions beyond the fingers, no finger ulcers, and no interstitial lung disease (ILD).[5]

In order to overcome the limitations of the ACR criteria, LeRoy et al.[6] formulated criteria for the limited forms of SSc which basically define a group of pre-SSc. According to the LeRoy criteria, patients with limited SSc must have Raynaud's phenomenon (RP) plus scleroderma-type nailfold capillary changes and/or autoantibodies.[7] However, they did not mention which other symptom/sign/laboratory/instrumental finding should be considered as an exclusion criterion for the diagnosis of limited SSc. The current validated or proposed criteria are not appropriate to make a very early diagnosis of SSc, and this implies that the diagnosis of SSc and, consequently, appropriate therapy is delayed until the appearance of skin involvement and/or clinically detectable internal organ involvement[8-10] when microvascular remodeling, tissue fibrosis, or atrophy are already irreversible.[11] This limits the possibility of an early treatment and the prevention of disease evolution and tissue damage, leading

to loss of function and decrease in the quality of life. Moreover, because of the changes in patient's appearance due to skin sclerosis, muscle atrophy, and joint contracture, it has also a substantial impact on the patient's emotional and psychological well-being.[12,13] For these reasons, SSc is considered as one of the greatest challenges in the management of rheumatic diseases.

According to the population-based studies, mild SSc may be a more frequent disease than has previously been suspected; therefore, the identification of very early SSc with an early diagnosis is of crucial importance.[11]

Very early diagnosis of systemic sclerosis: dream or reality? SSc is easy to diagnose when the disease has already evolved to obliterative vasculopathy, with skin fibrosis and significant end-organ damage. The clinical presentation may depend either on the extent of fibrotic changes and/or impaired blood supply caused by vascular changes. By the time of the onset of an organ-related symptom, the fibrotic/vascular involvement may have started several months or even years before.[11]

Very early stages of SSc are clinically characterized by the onset of RP, sclerodactily, and often by the presence of SSc-specific autoantibodies.[7] The definition of "early SSc" as a state characterized by RP, puffy fingers, disease-specific autoantibodies, and pathognomonic microvascular alteration detected by capillaroscopy (requiring at least 2, or better, all 3 items to be present) has been proposed.[14] Still today, SSc diagnosis is delayed several years following the onset of RP and several years after the onset of the first non-RP symptom. In a recent Delphi exercise, 4 signs/symptoms have been identified as necessary for the very early diagnosis of SSc: RP, puffy swollen digits turning into sclerodactily, specific SSc antibodies (anticentromere and antitopoisomerase-I antibodies), and abnormal capillaroscopy with scleroderma pattern.[15] RP and puffy swollen digits turning into sclerodactily were considered in the final analysis of the whole assembly of the European League Against Rheumatism Scleroderma Trials and Research members as "red flags" for the general practitioner leading to the suspect of a very early SSc and thus, to refer the patient to a specialist for the final diagnosis of very early SSc. Specific autoantibodies (anticentromere and antitopoisomerase-I antibodies) and nailfold capillaroscopy were considered as preferred diagnostic tools to finally define a patient suspected of very early SSc.

However, these early disease features are not specific for SSc, because other entities may also display a combination of these characteristics. At this point, doctors may face 2 challenges: 1) to confirm that a patient with these features is already affected by SSc or at least a condition within the scleroderma spectrum, including prescleroderma,[16] undifferentiated connective tissue disease,[17] or mixed connective tissue disease[18]; 2) to decide how to treat this patient – aggressively or wait and stand by. In reality, these decisions are compromised by a lack of agreement and validation of the criteria to define early disease and predictors of disease evolution.

Diagnostic and therapeutic standards vary widely across the global clinical community, and no consensus has been reached on the optimum approach to screening and diagnosis.[19] Patients with very early SSc are the target of the recently launched Very Early Diagnosis of Systemic Sclerosis (VEDOSS) program, which has been designed to diagnose SSc very early and to examine whether this may change the disease prognosis. The hypothesis is that the follow-up will allow us to define prognostic clinical or genetic markers during the patients' care.[14]

In recent studies, after an extended screening program during a mean (standard deviation) follow-up period of 11.2 (3.9) years, the prevalence of transition from primary to secondary RP, identified by diagnosis of an associated disease, was 14.9% of the cases.[20] Although patients with RP, autoantibodies, and SSc capillaroscopic pattern could be easily followed up, we still lack an agreement on the predictors that may allow us to identify patients that will develop an established disease.[21]

Patients must be followed up regularly even though the ideal frequency of such visits has not yet been established. Valentini et al.[22] clearly showed that the subclinical involvement in SSc is early, while the clinical signs of organ involvement may appear later. Furthermore, organ involvement is usually progressive and complications frequent, both in the limited and diffuse subsets of SSc.

Why is very early diagnosis mandatory? In SSc, severe organ-based complications are frequently observed including scleroderma renal crisis (SRC), sudden death, ILD and pulmonary arterial hypertension (PAH), digital ulceration [DU]. These complications produce a high case-specific mortality rate observed among patients with SSc.[21,23] For these reason, all efforts are now aimed at preventing the delay in diagnosis.

Scleroderma renal crisis Despite the use of angiotensin-converting enzyme inhibitors to prevent SRC, it occurs in 6% of SSc patients and in 10% to 15% of those with diffuse SSc. In SRC, 40% of the patients may require dialysis, and mortality at 5 years is from 30% to 40%. Patients at the greatest risk of developing SRC are those with diffuse cutaneous or rapidly progressive forms of SSc, a recent onset of SSc without evidence of RP, a recent treatment with high-dose corticosteroids, and the presence of tendon friction rubs.

The course of SRC is characterized by an abrupt onset of hypertension, acute renal failure, headaches, fever, malaise, hypertensive retinopathy, encephalopathy, and pulmonary edema. Laboratory tests may demonstrate hypercreatinemia, microangiopathic hemolytic anemia, thrombocytopenia, and hyperreninemia.

Renal crisis is also linked to a positive antinuclear antibodies speckled pattern, antibodies to RNA polymerase I and II, and an absence of anticentromere antibodies.[24]

Early diagnosis and treatment may thus be crucial in improving outcomes. In fact, SSc patients renal function has to be regularly controlled by laboratory test, creatinine clearance, and renal echo Doppler to exclude the presence of an increased renal resistance index or a reduction of renal blood flow.

Interstitial lung disease and pulmonary arterial hypertension   Pulmonary disease due to ILD or PAH is now the major cause of death,[25-27] with up to 30% of deaths directly associated with pulmonary fibrosis.[27]

PAH is defined as the mean pulmonary arterial pressure of 25 mmHg at rest with normal pulmonary capillary wedge pressure (<15 mmHg)[28]; its incidence is from 15% to 35% in patients with limited cutaneous SSc, usually as isolated PAH, and 30% in patients with diffuse cutaneous SSc, frequently associated with pulmonary fibrosis.[29]

In SSc, identification of PAH often occurs late with up to 81% of the patients categorized as New York Heart Association (NYHA) Class III or IV at the time of PAH diagnosis.[30]

Therefore, early detection of PAH is a challenge because its symptoms (dyspnea, fatigue, exercise intolerance) are nonspecific and overlap with those of other morbidities of SSc, including ILD and cardiomyopathy. Once established, severe PAH is difficult to treat and has poor prognosis.[31,32]

Identification of the risk factors or predictors of the development of PAH in individuals with SSc would allow an earlier diagnosis and institution of specific therapy for PAH at a time when it is most likely to be effective. For this reason, a simple score has been recently proposed, using routine clinical observations (age, forced vital capacity and lung diffusion capacity/alveolar volume [DL_{CO}/VA]), which accurately predict the risk of PAH in SSc.[33]

Regarding predictors, it has also been reported that the elevated levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP) predict the occurrence of PAH.[34] There is growing evidence that the BNP level might be a biomarker for PAH in terms of screening, diagnostic evaluation, evaluation of response to therapy, and prediction of disease severity.[35]

It has also been suggested that it is possible to identify "pre-PAH" or "early PAH" using accurate measures of the DL_{CO}/VA as a reflection of capillary gas exchange and of the NT-proBNP as a reflection of cardiac wall stress. Moreover, the combination of these 2 variables is a very strong predictor of the development of PAH. They recommend that SSc patients with both a DL_{CO} 70% and elevated NT-proBNP levels should be very carefully monitored. They suggest that such patients would constitute an appropriate target group for the investigation of early therapeutic intervention for PAH in a randomized trial.[35]

Digital ulcers   In some patients, particularly in those with limited SSc, ulcers are the most disabling complication, causing pain (especially when infected), limited function, digital resorption, and osteomyelitis.[36]

Various studies have revealed that among patients with SSc, from 15% to 25% have active DU[37] and 35% have active DU or have had DU in the past.[38] These numbers vary in different studies, possibly due to different geographical areas or different study methods and designs.[39,40]

The early detection of patients with high risk of developing DU could allow to introduce a preventive treatment and thus reduce morbidity and social costs.

Nailfold videocapillaroscopy (NVC) is an imaging technique for a microcirculation study, and it represents one of the most reliable tools for the classification and diagnosis of SSc and related conditions.[41,42]

Sebastiani et al.[43] have developed a capillaroscopic skin ulcer risk index that can predict the onset of new digital ulcers by using NVC in patients with SSc. Alivermini et al.[36] reported that the best independent DU predictors in SSc patients are interleukin-6 levels higher than 2 pg/ml, lupus anticoagulant positivity, and the presence of avascular areas on the NVC analysis. Their results could be useful for physicians in daily practice to identify which SSc patients have higher risk of developing skin ulcers during the course of the disease. This diffuse SSc subset, with lung and cardiopulmonary involvement, thrombophilia, and avascular areas on NVC, represents the major risk factor for the development of DU.[36]

Cardiac involvement   The presence of cardiac involvement in SSc is underestimated due to the occult nature of the signs and symptoms. Moreover, symptoms of cardiac manifestations are often attributed to noncardiac causes such as pulmonary, musculoskeletal, or esophageal involvement. More recent studies suggest that clinical evidence of myocardial disease may be seen in 20% to 25% of SSc patients.[44]

Clinical factors, such as age and systemic extent of disease, appear to correlate with cardiac rhythm disturbances observed by ambulatory electrocardiography, although there are conflicting data regarding the association between predictive factors of lung disease and the incidence of ventricular tachyarrhythmias. Interestingly, sex, duration of disease, extent of skin involvement, and the presence of serum anticentromere antibody do not appear to predict ventricular arrhythmias.[45]

Symptoms such as palpitations or syncope are predictive of electrocardiographic abnormalities in SSc patients.[46] Ambulatory electrocardiography is also useful for the risk stratification of SSc patients. Kostis et al.[45] reported that ventricular

tachycardia was associated with a 2-fold increase in the risk of death, whereas frequent ventricular ectopy defined as more than 100 premature ventricular contractions (PVCs) per 24 hours was associated with a 4-fold increase in the risk of death, and ectopy defined as more than 1000 PVCs per 24 hours was associated with a 6-fold higher risk of death.[45] Other risk factors of developing tachyarrhythmias are a prolonged QTc interval, heart rate variability, and PR interval prolongation.

In a study of 54 patients, 69% were found to have abnormalities on echocardiogram,[47] mainly elevated right ventricular systolic pressure, pericardial effusion, increased right ventricular dimension, and left atrial enlargement. In addition to structural defects, 24-hour ambulatory monitoring detected arrhythmias and conduction system abnormalities in SSc patients with or without symptoms.[48,49]

Magnetic resonance imaging (MRI) is a reliable and sensitive technique for early diagnosis of cardiac involvement in SSc and analysis of its mechanisms, including the inflammatory, microvascular, and fibrotic components. Compared with echocardiography, MRI appears to provide additional information by visualizing myocardial fibrosis and inflammation.[50]

Conclusions   Only prospective studies can lead to the validation of the provisional criteria presented above. This could help to reduce the gap between symptoms and diagnosis. The evaluation of patients with SSc should indeed include the assessment of the severity of each organ involvement, of functional impairments, and of the impact on the quality of life.

The DL_{CO}/VA, NT-proBNP, and nailfold capillaroscopy can be used to identify SSc patients who are at high risk for the development of PAH. This has important clinical implications as noninvasive tests (laboratory tests, pulmonary function tests, and echocardiography) may be used to identify high-risk patients who should undergo right heart catheterization.

In order to check cardiac involvement, SSc patients should be routinely monitored by ambulatory electrocardiography, echocardiography, and Holter electrocardiogram, and if necessary perform further exams (MRI, single-photon emission computed tomography).

Renal function has to be regularly controlled by laboratory test, creatinine clearance, and renal echo Doppler in order to prevent scleroderma renal crisis.

NVC (every 6 months or once a year) is suggested for all RP patients.

It is particularly important to confirm that the identified "red flags" can help us in the very early phase of the disease to track patients at risk for progressing to overt disease, using this "window of opportunity" to fight the disease at a still reversible phase by an appropriate treatment.

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Rozpoznanie bardzo wczesnej postaci twardziny układowej

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STRESZCZENIE

Twardzina układowa (*systemic sclerosis* – SSc) jest nieuleczalną przewlekłą chorobą autoimmunologiczną cechującą się dużą chorobowością i śmiertelnością. Obecne walidowane lub proponowane kryteria nie są przydatne do rozpoznawania bardzo wczesnych postaci SSc. Powoduje to, że rozpoznanie SSc, a w konsekwencji właściwe leczenie, jest opóźnione do czasu wystąpienia zmian skórnych i/lub dających się wykryć klinicznie zmian narządów wewnętrznych, kiedy to przebudowa mikrokrążenia, włóknienie tkanek lub zmiany zanikowe są już nieodwracalne.

W przeprowadzonej ostatnio analizie metodą Delphi wskazano 4 objawy/zmiany jako niezbędne do rozpoznania bardzo wczesnej postaci SSc: objaw Raynauda, obrzęk palców prowadzący do sklerodaktylii, występowanie przeciwciał przeciwjądrowych i swoistych przeciwciał (antycentromerowych i skierowanych przeciwko topoizomerazie 1) oraz nieprawidłowy obraz kapilaroskopowy o typie zmian twardzinowych. Chorzy z bardzo wczesną postacią SSc obejmowani są rozpoczętym ostatnio programem VEDOSS, którego celem jest bardzo wczesne wykrywanie choroby z jednoczesną oceną, czy wpływa ono na rokowanie. Mimo obserwacji chorych z objawem Raynauda, autoprzeciwciałami i zmianami kapilaroskopowymi, wciąż nie zostały poznane czynniki umożliwiające rozpoznanie pacjentów, u których rozwinie się zaawansowane stadium SSc.