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Opinion Article

Classification criteria of systemic sclerosis: Journey so far

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ABSTRACT

Systemic sclerosis (SSc) is a rare connective tissue disease of obscure etiology with heterogenous manifestations. In order to understand this disease and improve patient prognosis, various classification criteria have been proposed over time but as these criteria lack sensitivity and specificity, early identification of patients is still a difficult task. The improved understanding of disease pathogenesis has led to reanalysis and updating of existing classification criteria for SSc. Researchers are emphasising on the importance of nail fold capillaroscopy and SSc related auto antibodies as significant criteria for early diagnosis of SSc. These newer classification criteria need to be extensively used and validated before they gain universal acceptance.

Key words: Heterogenous; Nail fold capillaroscopy; Autoantibodies

INTRODUCTION

Systemic Sclerosis is a multi system, multistage connective tissue disease characterized by vasculopathy, fibrosis and degenerative changes in the skin and internal organs and production of autoantibodies [1]. This disease may involve one or many internal organs including heart,lungs,gastrointestinal tract. The spectrum of manifestations and prognosis of Systemic Sclerosis (SSc) is variable. Early identification of SSc patients is of great importance to delay the development of complications and to screen patients for severe organ involvement. In the last two decades,there has been a better understanding of the natural course of the disease and a remarkable progress in the diagnostic tests for Systemic sclerosis [2].

The diagnostic criteria for SSc are lacking,although there are several classification and subset classification criteria proposed for SSc which aid in diagnosis [3]. The Classification criteria are standardised criteria which help in differentiating patients with the disease in question from those without the disease. The basic utilization of classification criteria is for clinical trials and research studies but since they closely mimic the diagnostic criteria, they can be used as a basic tool in identifying patients in early stages of Systemic Sclerosis. The patients classified as having SSc are a subset of patients being diagnosed as having SSc, with diagnosis being more sensitive [4]. The classification criteria serve as important guidelines for differentiating SSc from various overlapping diseases on the basis of clinical and serological parameters. In this article, an attempt has been made to review the history of classification and subsetting of SSc with special emphasis on the recently proposed EULAR classification criteria.

In 1978, the first classification of SSc was proposed by Barnett [5], according to which there were three subsets: Type I, with skin changes involving only the fingers; Type II, with sclerosis limited to the forearms; and Type III, with diffuse skin involvement. A couple of years, after this attempt by Barnett, the first standard classification criteria for Systemic Sclerosis were developed by the American College of Rheumatology (ACR) in 1980 [6]. The ACR criteria have the advantage of being well researched and validated in a large population of patients along with 92% sensitivity and 96% specificity [7]. These are often used to diagnose patients of SSc [3]. According to these criteria, patient should have either one major or two out of three minor criteria.

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1. Major criteria: Scleroderma proximal to the digits, affecting limbs,face,neck or trunk
2. Minor criteria: At least two minor criteria out of the three:
   a. sclerodactyly
   b. digital pitted scarring
   c. bilateral basal pulmonary fibrosis

Drawbacks of ACR criteria:
1. The ACR criteria do not deal with the heterogeneity of SSc [5]
2. These criteria were developed by using patients with long standing disease so chances of missing early Systemic Sclerosis is high [8]
3. These criteria are insufficient to diagnose cases with limited form of SSc [2]
4. The characteristic nail fold changes of SSc, which are an important early feature in SSc, are not included in these criteria [9]
5. The diagnostic tests for autoantibodies which aid early diagnosis, have improved over the years [9].
6. Less sensitivity [7].

The second classification criteria were proposed by LeRoy in 1988 [10]. The main highlight of these criteria was that it differentiated the two main subsets of Systemic Sclerosis: Diffuse form of SSc (dcSSc) and Limited Cutaneous form of SSc (lcSSc.). The LeRoy classification is shown in Table 1 [6]. The main advantage of this classification is its ease of use in everyday practice and wide acceptance [7]. The drawback is that this classification is highly exclusive. There is an unsettling dilemma of whether the diffuse and limited forms are different diseases or represent different phenotypes of the same disease [5]. Another major drawback is that patients with early disease, without or with minimal skin changes and no internal organ involvement, do not fit in this classification [3].

The LeRoy classification was revised and a modified classification was proposed by LeRoy & Medsger in 2001 [5]. Table 2 shows the LeRoy & Medsger classification [10]. This classification differentiated Early SSc using nail fold capillaroscopy and SSc related autoantibodies and included an additional early or limited form of scleroderma, lSSc, to supplement the previously recognized lcSSc and dcSSc forms [5]. According to LeRoy and Medsger, adding nailfold capillary findings and anticentromere serology,improved the sensitivity of ARA classification, highlighting the key role played by these two features [9]. Despite its

Table 1: LeRoy's classification of systemic sclerosis

Diffuse cutaneous systemic sclerosis	Limited cutaneous systemic sclerosis
Short interval (<1 year) between onset of raynaud's phenomenon and the development of skin changes.	Long history of raynaud's phenomenon
Truncal and peripheral skin involvement	Limited skin involvement
Tendon friction rubs	
Lung, renal, diffuse gastrointestinal and myocardial involvement	Late onset pulmonary hypertension, calcinosis, telangiectasies
Scl-70 positive	Anticentromere antibody positive
Capillary drop out visible in nail folds	Dilated nail fold capillaries visible in nail folds

Table 2: LeRoy and Medsger classification criteria

Limited SSc (lSSc)	Limited cutaneous SSc	Diffuse cutaneous SSc
Raynaud's phenomenon objectively documented by :	Criteria for lSSc	Criteria for lSSc
1. Direct observation of any of the two :	Plus	Plus
a. Pallor (well demarcated whitening of acral skin)	Distal cutaneous	Proximal cutaneous
b. Cyanosis (dusky blueness which disappears on rewarming)	Changes	Changes
c. Suffusion (well demarcated redness)		
or		
2. Direct measurement of response to cold by:		
a. Abnormal widefield nailfold capillaroscopy		
b. Nielsen test or equivalent		
plus any one:		
SSc-type nailfold capillary pattern		
or		
SSc selective autoantibodies		
If Raynaud's Phenomenon is subjective only:		
both SSc capillary pattern and SSc selective autoantibodies (in titre > 1:100) are required to define lSSc		

SSc: Systemic sclerosis; lSSc: Limited cutaneous form of systemic sclerosis

advantages, this classification has not been validated [3]. The confusion in differentiating the two forms lSSc and lcSSc is another drawback of this classification [5].

In 2004, Maricq and Valter proposed a further set of classification criteria of SSc as shown in Table 3 [5]. This classification tries to subclassify the disease and incorporates new diagnostic technologies. The main drawback is that it has not been validated externally nor has it been tested in control population [7]. These criteria are quite complex and are not easy to apply making their wide acceptance difficult [5].

The need for revised criteria for SSc arose because of various reasons [8]:

1. The mere absence of cutaneous involvement does not exclude the diagnosis of SSc as it is a multiorgan disease with variable internal organ manifestations.
2. The immunological and vascular changes occur early in disease but are not given significance in the previous classifications.
3. Since 1980, significant advances have occurred in the understanding of disease pathogenesis, resulting in need for newer criteria.
4. No classification criteria so far has received universal acceptance.

Table 3: The Maricq–Valter subset classification

Type	Characteristics
I	Diffuse skin involvement proximal to elbows/knees; includes trunk
II	Intermediate skin involvement proximal to MCP/MTP, distal to elbows/knees; trunk not involved
III	Digital sclerodactyly only: meets ACR minor criteria, but excludes those without skin involvement
IV	'Scleroderma' sine scleroderma: capillary pattern or pitting scars and visceral involvement; no anticentromere antibodies; no telangiectasias
V	UCTD with scleroderma features; no anticentromere antibodies; no telangiectasias
VI	CREST, no skin involvement, or sclerodactyly only; telangiectasias are required with one or more other CREST feature; or anticentromere antibodies is required with any two or more CREST features
VII	Belongs to II and III respectively and includes CREST features
VIII	Belongs to II and III respectively but has no CREST features

UCTD: Undifferentiated connective tissue disease; ACA: Anticentromere antibodies; MCP/MTP: Metacarpophalangeal/metatarsophalangeal, CREST: Calcinosis, Raynaud's phenomenon, oesophagus dysfunction, sclerodactyly and telangiectasias

The revised SSc classification criteria should satisfy the following requirements [7]:

1. They should include the complete spectrum of SSc and should apply to patients that are early as well as late in the disease process.
2. They should include vascular, immunologic, and fibrotic manifestations.
3. They should be feasible in daily clinical practice and clinical studies.
4. They should be as close as possible to items used for diagnosis in clinical practice.
5. They should be more sensitive and specific than the previous criteria.

The newest criteria which has been proposed in 2013 is the ACR/EULAR classification. This classification includes one definitive criteria which is sufficient to make diagnosis of SSc and seven criteria with point system which are used if definitive criteria is not fulfilled. The total score is determined by adding the maximum weight (score) in each category. Patients with a total score of 9 are classified as having definite SSc. The ACR/EULAR 2013 criteria are shown in Table 4 and the definitions of items/sub-items for these criteria are given in Table 5 [4].

Advantages of ACR/EULAR criteria [3]:

1. These have greater sensitivity and specificity than the previous criteria. Sensitivity and specificity in the validation sample for EULAR criteria is 0.91 and

Table 4: ACR EULAR classification criteria

Item	Subitem	Weight/Score
Skin thickening of the fingers of both hands extending proximal to MCP joints (sufficient criteria)	-	9
Skin thickening of the fingers (only count the higher score)	Puffy fingers	2
	Sclerodactyly of fingers (distal to the MCP joints, proximal to the PIP joints	4
Fingertip lesions (only count the higher score)	Digital tip ulcers	2
	Fingertip pitting scars	3
Telangiectasia	-	2
Abnormal nailfold capillaries	-	2
Pulmonary arterial hypertension and/or interstitial lung disease	-	2
Raynaud's phenomenon	-	3
SSc-related auto-antibodies (anticentromere, anti-topoisomerase I, anti-RNA polymerase III)	-	3

Add to maximum weight in each category to calculate the total score. Patients having a total score of 9 or more are being classified as having definitive systemic sclerosis

Table 5: Defination of items in ACR EULAR classification

Item	Definition
Skin thickening	Skin thickening or hardening not due to scarring after injury, trauma, etc.
Puffy fingers	Swollen digits—a diffuse, usually nonpitting increase in soft tissue mass of the digits extending beyond the normal confines of the joint capsule. Normal digits are tapered distally with the tissues following the contours of the digital bone and joint structures. Swelling of the digits obliterates these contours. Not due to other causes such as inflammatory dactylitis
Fingertip ulcers or pitting scars	Ulcers or scars distal to or at the proximal interphalangeal joint not thought to be due to trauma Digital pitting scars are depressed areas at digital tips as a result of ischemia, rather than trauma or exogenous causes
Telangiectasia	Telangiectasiae are visible macular dilated superficial blood vessels, which collapse upon pressure and fill slowly when pressure is released. Telangiectasiae in a scleroderma-like pattern are round and well demarcated and found on hands, lips, inside of the mouth, and/or are large mat-like telangiectasiae. Distinguishable from rapidly filling spider angiomas with central arteriole and from dilated superficial vessels
Abnormal nailfold capillary pattern	Enlarged capillaries and/or capillary loss with or without pericapillary hemorrhages at the nailfold
Consistent with systemic sclerosis	May also be seen on the cuticle
Pulmonary arterial hypertension	Pulmonary arterial hypertension diagnosed by right-sided heart catheterization according to standard definitions
Interstitial lung disease	Pulmonary fibrosis seen on high-resolution computed tomography or chest radiography, most pronounced in the basilar portions of the lungs, or occurrence of "Velcro" crackles on auscultation, not due to another cause such as congestive heart failure
Raynaud's phenomenon	Self-reported or reported by a physician, with at least a 2-phase color change in finger (s) and often toe (s) consisting of pallor, cyanosis, and/or reactive hyperemia in response to cold exposure or emotion; usually one phase is pallor
SSc-related autoantibodies	Anticentromere antibody or centromere pattern seen on antinuclear antibody testing, anti– topoisomerase I antibody (also known as anti–Scl-70 antibody), or anti–RNA polymerase III antibody. Positive according to local laboratory standards

0.92 in comparison to 0.75 and 0.72 for the 1980 ACR classification criteria.
2. These criteria perform well even in patients with early SSc (less than 3 years).
3. These criteria combine the significant points of previous all classifications along with new criteria.
4. These criteria include newer advances in the diagnostic techniques like specific serum autoantibodies.
5. The present classification does not require any computing device, hence can be easily used in individual subjects.
6. ACR/EULAR criteria have an advantage as it uses two standards for testing and validation of the proposed system.

CONCLUSION

To facilitate early diagnosis in SSc, improving patient care and prognosis, there is need for a validated and well accepted set of classification criteria for SSc. There is still lack of an incontrovertible test or criteria for SSc. Till that time, the classification criteria for SSc remains an evolving issue, needing more scientific research.

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