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Systemic Sclerosis

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Abstract Systemic sclerosis (SSc) is a chronic disease of unknown etiology, and its classification as a systemic autoimmune rheumatic disease (SARD) is supported by clinical and experimental observations that include the presence of autoantibodies (AAs) and autoreactive T cells. Although some AAs are specific markers for the disease, there has not been widespread adoption of them as specific classification criteria. The application of classification criteria is further hampered by the recognition that diagnosis of SSc encompasses a wide variety of clinical features that prompts the classification of the condition into a number of disease subsets. For practical purposes, most clinicians subclassify the disease as limited cutaneous SSc (lcSSc) or diffuse cutaneous SSc (dcSSc). As diagnostic technologies rapidly evolve and clinicians consider designer therapies for this condition, the development and universal adoption of clinical classification criteria will be a significant challenge.

Keywords Systemic sclerosis · scleroderma · classification · criteria · autoantibodies

Systemic sclerosis (SSc) is a connective tissue disorder characterized by endothelial dysfunction, fibrosis, and the production of autoantibodies (AAs). Excessive collagen deposition results in skin thickening and changes in internal organs that include the lung, vasculature, gastrointestinal tract, and kidney. Endothelial damage leading to vascular dysfunction is manifest as Raynaud's phenomenon, digital ulceration and gangrene, pulmonary arterial hypertension, and renal vascular damage. SSc is usually subclassified as limited or diffuse depending on the extent of skin involvement. The distinction between limited and diffuse SSc varies, but most authorities would concur that patients with truncal and acral involvement have diffuse disease whereas changes distal to the metacarpophalangeal and metatarsophalangeal joints are consistent with limited disease. There is debate over the degree of acral involvement that constitutes limited versus diffuse disease (1). Typically, patients with limited SSc have a more insidious disease onset, and they describe Raynaud's phenomenon for some years prior to the onset of sclerodactyly. In contrast, in those with diffuse SSc the skin thickening tends to more closely coincide with the onset of Raynaud's phenomenon and the disease course is more acute, with most internal organ involvement occurring within 5 years (2). Tables 6.1 and 6.2 summarize clinical features of the disease in the diffuse and limited subsets.

Epidemiology

SSc occurs worldwide, and the incidence and prevalence rates show a wide variation depending on the geographic location, disease definition, classification criteria and methods of case selection. There is evidence that the incidence and prevalence has increased from 2.7 new cases per million to 18.7 and from 138 total cases per million to 660 respectively over a 25-year interval. The higher prevalence rates of approximately 230 cases per million have been reported in the USA and South Australia. The disease occurs more frequently in women than men (4:1), although this ratio is more pronounced in younger patients and less so in adults aged >50 years. The diagnosis of the disease is most commonly made in individuals in the fifth decade but can begin in childhood or septuagenarians. The disease onset is earlier in African-American women than European American women and is more likely to be diffuse disease (reviewed in ref 3). The proportion of (lcSSc) versus (dcSSc) also varies by geographic region and racial group. This is also true of AA markers (discussed below), all giving strong indications that host and environmental factors play a role in disease pathogenesis and expression. Environmental factors of interest associated with an increased risk of

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TABLE 6.1. Clinical features helpful in classification of systemic sclerosis.[a]

Limited cutaneous SSc	Diffuse cutaneous SSc
Raynaud's phenomenon alone for years	Delayed Raynaud's or same as skin
Rare constitutional symptoms	Severe constitutional symptoms
Minimal arthralgias	Arthralgias, carpal tunnel
Puffy fingers	Puffy hands and legs
Telangiectasias and calcinosis (late)	Palpated tendon friction rubs
Skin thickening limited to hands and face	Skin thickening progresses from fingers to trunk rapidly
GI and mild pulmonary fibrosis	GI and pulmonary fibrosis common
Rare heart and kidney	Heart and kidney potentially severe
Anti-centromere antibody	Anti-topoisomerase I (Scl-70) Anti-RNA polymerase III Anti-fibrillarin

GI, gastrointestinal.
[a] Adapted from ref 2 with permission from Elsevier.

developing the disease include exposure to particulate silica, trichloroethylene and other organic solvents, and heavy metals such as mercury.

TABLE 6.2. Comparison of features in SSc patients with limited cutaneous SSc and diffuse cutaneous SSc.[a]

Feature	Limited cutaneous SSc	Diffuse cutaneous SSc
Demographic		
Age <40 years at onset (%)	50	35
Sex: female (%)	85	75
Duration of symptoms before diagnosis (years)	8.5	2.0
Cumulative survival 10 years after diagnosis (%)	75	65
Organ system involvement (%)		
Skin thickening	95	100
Telangiectasias	80	30
Calcinosis	50	10
Raynaud's phenomenon	95	85
Arthralgias or arthritis	60	80
Tendon friction rubs	3	65
Joint contractures	45	85
Myopathy	10	20
Esophageal hypomotility	75	75
Small intestine hypomotility	25	25
Pulmonary fibrosis	35	45
Pulmonary hypertension	10	<1
Congestive heart failure	5	15
Renal crisis	1	20
Laboratory data		
Antinuclear antibody	95	95
Anti-centromere antibody	50	<5
Anti-topo I	18	30
Anti-RNAP III	2	25
Anti-fibrillarin	<1	12
Anti-PM/Scl	5	15

[a] Adapted from ref 2 with permission from Elsevier.

Genetics

The relative risk of developing SSc, if a first degree relative has it, is a remarkable 13%, although the absolute risk in individual family members is much lower at <1% (3). There is evidence that serological but not clinical subsets of SSc are most highly linked to HLA class II genes (3). A number of other genetic loci have also been identified, and these are thought to be associated with distinct SSc phenotypes based on AA profiles rather than SSc as a single disease entity (3). If these observations are substantiated, they will have implications for design and approach to therapeutic interventions. In the past, there has been considerable interest in SPARC (secreted protein, acidic and rich in cysteine), PTPN22 that (encodes the lymphoid-specific tyrosine phosphatase nonreceptor type 2), and allograft inflammatory factor 1 (AIF1) (reviewed in ref 3). Recent studies have focused on friend leukemia integration 1 (Fli1), a transcription factor that is dysregulated in SSc skin and dermal blood vessels, and appears to play a pathological role in SSc skin fibrosis and vessel degeneration (reviewed in ref 3). Whether these abnormalities are related to genetic polymorphisms in the Fli1 pathway or to epigenetic mechanisms requires clarification.

Laboratory Findings

Laboratory findings vary according to internal organ involvement, but in the absence of acute progressive disease, they may be within the normal range. Elevated erythrocyte sedimentation rates and reduced complement levels have been observed in patients with more active disease (4). Other specific laboratory changes are coincident with organ involvement. For example, acute renal crisis may be marked by an elevated serum creatinine, evidence of hemolysis, and electrolyte disturbance.

Serological Markers

AAs occur in over 95% of patients with SSc, and to date, there are more than 30 AAs associated with SSc (5). The majority of patients have AAs directed to nuclear antigens, and these have specific clinical associations. Anti-centromere (CENP) antibodies occur in 20–40% of patients and are most commonly associated with limited SSc, ischemic digital loss, calcinosis, and pulmonary hypertension. Anti-topoisomerase I antibodies occur in 9–20% of patients and are associated with diffuse SSc, more severe disease, pulmonary fibrosis, and increased mortality. Anti-fibrillarin (U3 ribonucleoprotein) antibodies are reported to be highly specific for SSc, but in most SSc cohorts the prevalence is less than 12%. Although all these

antibodies have a high specificity, their low sensitivity means that on their own they are not a useful screen for SSc. Other AAs reported to be relatively specific for SSc and currently available in specialized clinical laboratories include RNA polymerase III (RNAP III), which is identified in 5–25% of SSc sera and has been associated with significant geographic variability and with renal crisis and pulmonary hypertension (reviewed in refs 5 and 6). Antibodies to the polymyositis/scleroderma (PM/Scl) antigens are seen in 14–20% of SSc patients, and most commonly, they identify a subset of patients with overlapping features of SSc and PM (7). There are other, less specific AAs associated with SSc that are also reported to have specific clinical associations, but, at present, they are of limited diagnostic utility.

Recently, a promising new specific AA directed against the platelet-derived growth factor receptor has been identified, and preliminary studies suggest that it is relatively specific for SSc (8 and references therein). However, these studies were based on a functional assay, which is currently not easily adaptable to the clinical setting.

Classification Criteria

There are no universally accepted classification criteria for SSc (reviewed in ref 9). This can be attributed to several factors: (a) rarity of the disease, (b) the absence of a specific diagnostic test, (c) debate regarding subclassification based on the extent of skin involvement, and (d) debate as to whether the limited and diffuse forms of SSc are continuums of one disease or are manifestations of different pathological processes. Despite many clinical similarities, differences in outcome, serology, and genetics support the concept that they may be two separate disease processes.

The two major forms of classification criteria currently in use are those that distinguish SSc from other forms of disease and those that also incorporate some degree of subclassification. Discussion in this chapter will be limited to the American College of Rheumatology (ACR) criteria and more recent classification criteria, as well as a selection of the more influential published subclassification criteria. The ACR classification criteria were designed to differentiate SSc from other forms of disease, and initial external validation recorded high levels of sensitivity and specificity (Table 6.3), (10). Unfortunately, subsequent testing in other disease registries led to the appreciation that these criteria lacked sensitivity, particularly in identifying patients with limited SSc (1). In addition, diagnostic techniques have advanced since their development, and there is growing support to include specific tests for antinuclear antibodies (ANAs) and nailfold capillaroscopy (reviewed in ref 5). Lonzetti et al. showed that in their cohort of French-Canadian patients the diagnostic value of the ACR criteria could be improved substantially by the addition of ANA and nailfold capillaroscopy evaluations (11). It is widely accepted that the ACR classification criteria are in need of an update, but they remain the most widely cited criteria to receive extensive external validation.

TABLE 6.3. 1980 ACR preliminary classification criteria for systemic sclerosis.[a]

1. Proximal scleroderma, skin involvement extending proximal to metacarpophalangeal joints (major criterion)
2. Sclerodactyly, digital pitting scars of fingertips or loss of substance of the distal fingerpad, and bibasilar pulmonary fibrosis (minor criteria)
3. One major or two or more minor criteria required

[a] Adapted from ref 10.

More recently, Nadashkevich et al. proposed an updated classification set that included the presence of AAs but did not include nailfold capillaroscopy (12). These criteria were first derived from the study of a Ukrainian cohort of SSc patients, and other connective tissue diseases (CTDs) were used as comparative groups. The eight criteria derived from the first phase of the study were subsequently tested in a population of 99 Canadian SSc patients and 138 CTD controls. Findings were promising, yielding a 99% sensitivity and 100% specificity (12). However, these criteria have not been widely adopted, possibly because they do not include subclassification of SSc.

Subclassification Criteria

While the need to differentiate SSc from other forms of disease is important, an improved understanding of the disease pathogenesis and the differing outcomes associated with different presentations of the disease has led to the recognition that subclassification of SSc can provide additional crucial information in terms of (a) prognosis in the routine clinical setting, (b) comparison between disease registries, and (c) a guide to emerging therapies. To date, there are 14 published subclassification criteria sets for SSc each proposing two to six separate categories (13), which are generally based on the degree of skin involvement. The majority of survival studies based on the degree of skin involvement suggest that there is no statistically significant differential survival in the three subgroup category, whereas differences in outcome using the two group subclassification set are well recognized (1, 13).

The two subset criteria first proposed by Le Roy in 1988 (14) and later published in modified form in 2001 (Table 6.4) (15) have been the most influential of the subclassification criteria groups. Categories are separated based on the degree of skin involvement, with the later criteria incorporating AAs and nailfold capillaroscopy changes. The 1988 criteria have been widely adopted, but the amended criteria have not been extensively utilized and require further validation. In addition, within these criteria diagnosis requires the presence of Raynaud's phenomenon, something that is not universally present, particularly at the onset of diffuse SSc.

TABLE 6.4. LeRoy and Medsger revised criteria for the classification of systemic sclerosis (SSc).[a]

Limited SSc	Raynaud's phenomenon (objective documentation) *Plus any one:* SSc-type nailfold capillary pattern or SSc selective autoantibodies *Or:* Subjective Raynaud's phenomenon *Plus both:* SSc-type nailfold capillary pattern and SSc selective antibodies
Limited cutaneous SSc	Criteria for limited SSc *plus* distal cutaneous changes
Diffuse cutaneous SSc	Criteria for limited SSc *plus* proximal cutaneous changes
Diffuse fasciitis with eosinophilia	Proximal cutaneous changes without criteria for limited SSc or limited cutaneous SSc

[a] Adapted from ref 15.

Maricq and Valter proposed a more complex subclassification that includes six different categories (16). Once again, the primary separation was based on the degree of skin involvement into three primary categories. Three additional categories are incorporated: (a) Scleroderma sine scleroderma, (b) features of mixed CTDs, and (c) a final group conforming to CREST phenomena but without sufficient changes to be incorporated into the three major skin change groupings. Nailfold capillaroscopy and AAs have been included in these criteria, but the AAs were limited to the presence or absence of CENP as detected by indirect immunofluorescence. As discussed above, CENP antibodies are now known to be one of four or five AAs that have relatively high specificity for SSc. In addition, the advent of multiplexed AA detection has provided a rapid and accurate way of detecting multiple AAs in a single serum sample, a feature which could change current AA paradigms (17). When applied to their database of 165 patients, they were able to show differential clinical outcomes. But in its current form it is difficult to use outside specialized tertiary research settings.

Treatment Options

Treatment options for SSc are still limited to treating specific aspects of organ involvement. Therapies designed to switch off the disease process, such as bone marrow transplantation (18), remain in their infancy. Clinical outcomes with therapies directed against profibrotic mediators, such as connective tissue growth factor and transforming growth factor-β, are in progress. Promising results have been reported with bosentan, a dual endothelin receptor antagonist, which has been shown to improve pulmonary arterial hypertension and digital ulceration (reviewed in ref 19). Proteomic and metabolomic approaches are identifying other common mediators that are potential therapeutic targets, but it is not known if this will result in improved.

Considerations and Future Directions

The wide use and application of classification criteria, particularly the inclusion of AAs into current and future criteria, is met by challenges and issues that must be carefully considered (Table 6.5). First, although classification criteria were clearly devised to standardize the classification of various diseases into uniform groups for research purposes, there appears to be an emerging divergence of clinical diagnostic nomenclature away from current classification criteria. One reason for this is that diagnostic technologies in imaging and serology are moving at such a fast pace and many clinicians are using these new technologies while classification criteria lag behind. It is clear that if classification criteria are to maintain a meaningful role, they will need to be revised and updated more frequently. Second, it is also clear that classification criteria must take into consideration the age of onset of the disease because the onset of SARDs (SARDs) in children or in the elderly often does not follow the clinical picture that is seen in adults. Third, classification criteria need to take into account genetic, racial, and geographic factors. It is becoming clear that the impact of geographic and ethnic variables have a significant impact on the spectrum of features seen in any of the SARDs. Classification criteria must take these variables into consideration to avoid a bias to a particular form of Scl in a given geographic setting. Fourth, diagnostic serology is rapidly moving to array technologies that provide a broad spectrum and wealth of AA, proteomic, genomic, and metabolomic data. In considering which AA might be included in a given classification criteria, it is important to recognize that the majority of SSc patients have more than one AA. While antibodies to CENP, topo I, and fibrillarin tend to be independent variables, the inclusion of other AAs such as PM/Scl or RNAP III will lead to a situation where a patient will have more than one AA. To avoid weighting the classification to serological markers, it will likely be useful to combine AA into a single criterion, an approach taken by Nadashkevich et al. (12). The rapidly emerging

TABLE 6.5. Challenges that must be considered in the inclusion of autoantibodies into classification criteria for systemic sclerosis.

- Divergence of classification criteria from diagnostic practice
- *Age*: Maybe one size (autoantibody) does not fit all
- Genetics/racial/geographic factors
- Early and late antibodies and response to therapy
- Impact of array technologies
  - Most SARD patients have >1 autoantibody
- Impact of the "omics":
  - genomics, ribonomics, proteomics, metabolomics leading to *Theranostics* or designer therapy
- Will disease classification survive as we know it?
- What about: protective, pathogenic, and prognostic autoantibodies
- Standardization

fields of genomics, proteomics, and metabolomics will also bring information to bear that has the potential to markedly improve classification criteria, especially if subclassification into disease subsets is considered a desirable clinical parameter. The wealth of information provided by these technologies and their application to therapeutics in an expanding field of medicine referred to as "personalized medicine" and "theranostics" (20) raises the possibility that classification criteria may not survive if patients are subdivided into small clinical groups based on single-nucleotide polymorphisms (SNPs) and other genetic markers, cytokine, lymphokine, AA, and metabolite profiles. Last, despite enthusiasm for the potential role for including AA or any of the other biomarkers referred to above in classification criteria of the future, the daunting challenge of standardization looms large. At present, classification criteria of SARD that include AAs are threatened by the lack of standardization of reagents and the assays used to detect them. For example, the sensitivity and specificity of any AA result are highly dependent on the assay used and the reagents used to standardize that assay. Hence, if AAs and other biomarkers are going to become valid biomarkers in classification criteria, there needs to be a stronger and coordinated effort to standardize the reagents and kits used for their detection.

In summary, published classification and subclassification criteria reflect our evolving understanding of SSc pathogenesis. With the available evidence, several conclusions can be drawn regarding the requirements of updated criteria:

1. Differential clinical outcomes within the SSc spectrum emphasize the need for a set that provides some form of subclassification to guide outcome and future treatment options as well as allowing differentiation from other diseases.
2. It is likely that the degree of skin involvement will remain a major differentiating factor and the majority of survival evidence supports a two subset system.
3. AAs have been shown to provide additional important information regarding prognosis and may also guide in the identification of early disease.
4. Nailfold capillaroscopy has some utility in diagnosis and classification, but its application remains highly specialized. This will need careful consideration if it is to be incorporated into future classification criteria.
5. For widespread acceptance, there will need to be international consensus for testing of the criteria and also for standardization of diagnostic assays.

References

1. Walker JG, Pope J, Baron M, Leclercq S, Hudson M, Taillefer S, Edworthy SM, Nadashkevich O, Fritzler MJ. The development of systemic sclerosis classification criteria. *Clin Rheumatol* 2007; 26: 1401–1409.
2. Steen VD. Clinical manifestations of systemic sclerosis. *Semin Cutan Med Surg* 1998; 17: 48–54.
3. Mayes MD, Trojanowska M. Genetic factors in systemic sclerosis. *Arthritis Res Ther* 2007; 9 Suppl 2: S5.
4. Valentini G, Della Rossa A, Bombardieri S, Bencivelli W, Silman AJ, D'Angelo S, Cerinic MM, Belch JF, Black CM, Bruhlmann P, Czirják L, De Luca A, Drosos AA, Ferri C, Gabrielli A, Giacomelli R, Hayem G, Inanc M, McHugh NJ, Nielsen H, Rosada M, Scorza R, Stork J, Sysa A. European multicentre study to define disease activity criteria for systemic sclerosis. II. Identification of disease activity variables and development of preliminary activity indexes. *Ann Rheum Dis* 2001; 60: 592–598.
5. Walker JG, Fritzler MJ. Update on autoantibodies in systemic sclerosis. *Curr Opinion Rheum* 2007; 19: 580–591.
6. Santiago M, Baron M, Hudson M, Burlingame RW, The Canadian Scleroderma Research Group, Fritzler MJ. Antibodies to RNA polymerase III in systemic sclerosis as detected by an ELISA. *J Rheumatol* 2007; 34: 1528–1534.
7. Mahler M, Raijmakers R. Novel aspects of autoantibodies to the PM/Scl complex: clinical, genetic and diagnostic insights. *Autoimmun Rev* 2007; 6: 432–437.
8. Baroni SS, Santillo M, Bevilacqua F, Luchetti M, Spadoni T, Mancini M, Fraticelli P, Sambo P, Funaro A, Kazlauskas A, Avvedimento EV, Gabrielli A. Stimulatory autoantibodies to the PDGF receptor in systemic sclerosis. *N Engl J Med* 354: 2667–2676.
9. Walker JG, Barnabe C, Fritzler MJ. Autoantibodies, classification criteria and diagnosis of systemic autoimmune rheumatic diseases. In: Conrad K, Chan EKL, Fritzler MJ, Sack U, Shoenfeld Y, Wiik A (eds): *From Etiopathogenesis to the Prediction of Autoimmune Diseases: Relevance of Autoantibodies*. Lengerich, Germany, Pabst Science Publishers, 2007, pp. 352–369.
10. Masi AT, Rodnan GP, Medsger T, Jr., Altman RD, D'Angelo WA, Fries JF, LeRoy EC, Kirsner AB, Mackenzie AH, McShane DJ, Myers AR, Sharp GC. Preliminary criteria for the classification of systemic sclerosis (scleroderma). *Arthritis Rheum* 1980; 23: 581–590.
11. Lonzetti LS, Joyal F, Raynauld JP, Roussin A, Goulet JR, Rich E, Choquette D, Raymond Y, Senécal JL. Updating the American College of Rheumatology preliminary classification criteria for systemic sclerosis: addition of severe nailfold capillaroscopy abnormalities markedly increases the sensitivity for limited scleroderma. *Arthritis Rheum* 2001; 44: 735–736.
12. Nadashkevich O, Davis P, Fritzler MJ. A proposal of criteria for the classification of systemic sclerosis. *Medical Science Monitor* 2004; 10: 615–621.
13. Johnson SR, Feldman BM, Hawker GA. Classification criteria for Systemic Sclerosis subsets. *J Rheumatol* 2007; 34: 1855–1863.
14. LeRoy EC, Black C, Fleischmajer R, Jablonska S, Krieg T, Medsger TA, Rowell N, Wollheim F. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. *J Rheumatol* 1988; 15: 202–205.

15. LeRoy EC, Medsger TA, Jr. Criteria for the classification of early systemic sclerosis. *J Rheumatol* 2001; 28: 1573–1576.
16. Maricq HR, Valter I. A working classification of scleroderma spectrum disorders: A proposal and the results of testing on a sample of patients. *Clin Exp Rheumatol* 2004; 22: S5–S13.
17. Fritzler MJ. Advances and applications of multiplexed diagnostic technologies in autoimmune diseases. *Lupus* 2006; 15: 422–427.
18. Dazzi F, van Laar JM, Cope A, Tyndall A. Cell therapy for autoimmune diseases. *Arthritis Res Ther* 2007; 9: 206.
19. Denton CP. Therapeutic targets in systemic sclerosis. *Arthritis Res Ther* 2007; 9 Suppl. 2: S6.
20. Bissonnette L, Bergeron MG. Next revolution in the molecular theranostics of infectious diseases: microfabricated systems for personalized medicine. *Expert Rev Mol Diagn* 2006; 6: 433–450.