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Editorial

More Than Skin Deep: Moving From a Skin-Based Phenotypic Model to Molecular Classification of Systemic Sclerosis

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Systemic sclerosis (SSc) is a multisystemic connective tissue disease, characterized by vasculopathy and fibrosis of the skin and visceral organs. It is conventionally classified according to the extent of skin fibrosis into limited cutaneous (lcSSc) and diffuse cutaneous (dcSSc) forms, based on the seminal article of LeRoy et al in 1988.[1] According to this classification, lcSSc is characterized by limited skin thickening not extending beyond the elbows and knees, and an association with CREST (calcinosis, Raynaud phenomenon [RP], esophageal dysmotility, sclerodactyly, and telangiectasia) syndrome and pulmonary arterial hypertension (PAH), whereas dcSSc is characterized by proximal and truncal skin thickening, which is rapidly progressive, and greater association with interstitial lung disease (ILD) and scleroderma renal crisis (SRC).[1] However, this skin-based phenotypic model was developed at a time when the molecular and/or serological profiles of most autoimmune and connective tissue diseases were not well defined. Over the past 2 decades, conditions such as idiopathic inflammatory myopathies have been increasingly redefined by serological profiling, in which myositis-specific autoantibodies are identified to diagnose, prognosticate, and guide treatment decision making.

In this article, we highlight the inherent limitations of the conventional skin-based phenotypic model of SSc and suggest that it is perhaps time to adopt a serology-centric classification of SSc that better predicts distinctive clinical syndromes comprising skin and other organ-specific manifestations.

Limitations of the conventional skin-based phenotypic model of SSc

There are several shortcomings of the lcSSc and dcSSc dichotomy that merit consideration. First, the skin-based classification does not account for early SSc, which is typically characterized by RP, scleroderma pattern on nailfold capillaroscopy, and/or SSc-specific antibodies described in both the LeRoy and Medsger criteria as well as the very early diagnosis of systemic sclerosis (VEDOSS) criteria, with the latter also including puffy fingers and positive antinuclear antibodies (ANA).[2,3] In general, early cases of SSc are notoriously difficult to diagnose due to nonspecific symptoms, such that the reported median time to SSc diagnosis from initial RP onset in 1 study was 3 years.[4] Delayed diagnosis, especially of early disease by nonrheumatologists, may therefore be perpetuated by a preoccupation with the conventional lcSSc/dcSSc model. Second, there is the entity of SSc sine scleroderma (ssSSc) that accounts for 9% of all SSc cases.[5] In ssSSc, patients have visceral fibrosis without clinically detectable skin thickening at diagnosis, although up to 28% of cases subsequently evolve into either the lcSSc or dcSSc subtype of skin involvement.[6] Commonly used criteria to classify ssSSc described by Poormoghim et al involves vasculopathy in the form of RP, digital ischemia, or abnormal nailfold capillaroscopy, with positive ANA and at least 1 visceral manifestation (cardiac, lung, renal, gastrointestinal) associated with SSc.[7] Third, the elbow and knee cutoff for assessing skin extent in lcSSc and dcSSc is arbitrary, with in vitro studies showing that clinically uninvolved skin in patients with SSc can actually be pathological, with abnormal endothelial activation and procollagen production.[8] Fourth, it is not uncommon for patients with SSc to have overlap autoimmune conditions that are diagnosed based on clinical and serological profiles, which would not be accounted for in the skin-based phenotypic model. It is reported that approximately 6% have concomitant rheumatoid arthritis or other connective tissue disorders such as systemic lupus erythematosus and Sjögren disease; 6% have overlap polymyositis[9]; and 0-12% have overlap antineutrophil cytoplasmic antibody–associated (primarily antimyeloperoxidase–positive) vasculitis.[10]

Advantages of a serology-based molecular classification model in SSc

A molecular classification based on a serological profile (Figure) may better describe the expected clinical syndromes and disease trajectory than the conventional skin-based phenotypic model for several reasons.

First, the differences in clinical phenotypes between lcSSc and dcSSc, although relevant, are strongly influenced by their underlying serological profiles. There is a higher incidence of PAH in lcSSc attributable to the higher prevalence of anticentromere antibodies, whereas the proclivity for ILD in dcSSc

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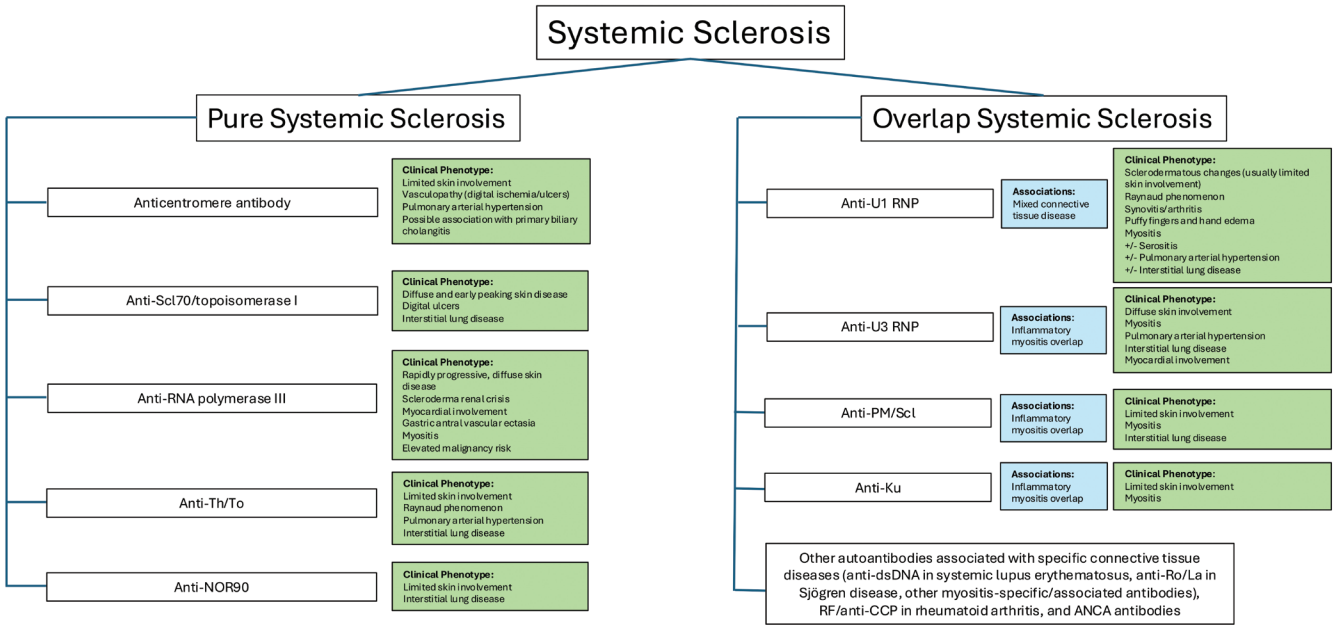

Figure. Proposed molecular classification of systemic sclerosis. Anti-CCP: anticyclic citrullinated peptide; ANCA: antineutrophil cytoplasmic antibodies; RF: rheumatoid factor.

is mediated by the higher prevalence of anti-Scl70 antibodies, and that of SRC by anti-RNA polymerase III (anti-RNAP3).[11] From a cohort study of patients with SSc from the International European Scleroderma Trials and Research group (EUSTAR) database, 1770 patients were classified into ssSSc, lcSSc, and dcSSc skin phenotypes, each having a different clinical and serological profile.[5] PAH was detected in 15% of ssSSc, 24% of lcSSc, and 29% of dcSSc; ILD was identified in 50% of ssSSc, 57% of lcSSc, and 75% of dcSSc; and SRC was present in 3% of ssSSc, 2% of lcSSc, and 5% of dcSSc.[5] Among patients with ssSSc, lcSSc, and dcSSc, the prevalence of anticentromere antibodies (ACA) was 62%, 42%, and 16%, respectively; anti-Scl70 antibodies 17%, 40%, and 61%, respectively; and anti-RNAP3 antibodies 4%, 5%, and 13%, respectively.[5]

Regardless of the extent of skin involvement, patients with ACA would generally have a more vasculopathic phenotype associated with recurrent digital ischemia/ulcers and a high incidence of PAH, milder skin disease, and lower risk of ILD and SRC.[12-13] In contrast, those with anti-Scl70 antibodies tend to have a fibrotic phenotype, with early-peaking skin thickening and > 75% of cases developing significant lung fibrosis within the first 3 years of disease onset.[12,13] Finally, patients with anti-RNAP3 antibodies are expected to have rapidly progressive skin disease and significant risk of SRC.[13] Additionally, patients with anti-RNAP3 antibodies tend to have greater propensity for myocardial involvement, gastric antral vascular ectasia, myositis, and increased cancer risk, although lung involvement is surprisingly lower.[12-15] Anti-PM/Scl and anti-Ku are myositis-associated antibodies that predict the phenotype of SSc–inflammatory myositis overlap,[9] with anti-PM/Scl also associated with ILD.[14] Both anti-U1 RNP and anti-U3 RNP antibodies are associated with PAH, with anti-U1RNP being a prerequisite antibody for mixed connective tissue disease.[13] Anti-U11/U12 RNP is associated with ILD.[14] Separately, anti-Th/To and anti-NOR90 antibodies are associated with PAH and pulmonary fibrosis, respectively.[13]

Serological profiling in SSc predicts distinct clinical phenotypes and patterns of organ involvement, enabling tailored immunosuppressive strategies and targeted surveillance for disease-related complications. For example, for patients with SSc, Komura described specific clinical monitoring bundles linked to their underlying autoantibody profiles.[13] In the described framework, patients with ACA-positive SSc would benefit from regular transthoracic echocardiographic monitoring for PAH; those with anti-Scl70 antibodies would need more frequent monitoring of lung function tests and high-resolution computed tomography of the thorax for development of ILD; and patients with anti-RNAP3 antibodies need stringent home blood pressure monitoring, regular assessments of renal function, and avoidance of glucocorticoids (especially at doses equivalent to prednisolone ≥ 15 mg/day) that can precipitate SRC.[15] Likewise, those with antibodies associated with overlap disease would need monitoring for the evolution of clinical syndromes (eg, sicca symptoms, serositis, inflammatory arthritis, myositis) associated with the overlapping disease that require distinct treatments.

Toward a robust clinical-molecular precision medicine model in SSc

Although a serology-based framework may offer advantages over the traditional skin-based phenotyping model in SSc, the ideal classification system in a future precision medicine landscape will likely integrate both clinical and molecular data. This would include patient demographics, premorbid characteris-

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tics, cutaneous and internal organ manifestations, nailfold capillaroscopy findings, and molecular signatures at the genetic and proteomic (including autoantibody) levels to facilitate more precise prognostication and therapeutic stratification. At the clinical level, poor prognostic factors that predict mortality in SSc include older age, male sex, African American and Asian race, dcSSc subtype, and visceral (cardiac, pulmonary, and renal) involvement.[16,17] Nailfold capillaroscopy is a convenient bedside test that not only can be performed for diagnostic purposes but also can identify poor prognostic patterns such as reduced capillary density (< 7 capillaries/mm) and active/late scleroderma patterns.[18] These prognostic patterns can predict disease progression and more severe manifestations (ie, worse skin fibrosis, digital ulcers, calcinosis, pulmonary hypertension, and ILD).[18]

At the molecular level, aside from the known SSc-specific autoantibodies that are good clinical biomarkers but have questionable roles in direct pathogenesis,[15] studies have identified in SSc several putative functional pathogenic autoantibodies, which bind to cognate (potentially targetable) autoantigens that exert agonistic or antagonistic effects on molecular pathways implicated in SSc pathogenesis.[19] These include antiendothelial cell antibodies, which promote fibroblast survival; autoantibodies against angiotensin II type 1 receptor and endothelin-1 type A receptor, which mediate SSc vasculopathy; antimuscarinic type 3 receptor antibodies, which drive autonomic dysfunction and gastrointestinal manifestations; and autoantibodies against platelet-derived growth factor (PDGF) receptor, which affects PDGF signaling and fibrosis.[19] However, the utility of these molecular markers is currently limited by the lack of high-fidelity laboratory assays and insufficient validation of their functional and clinical significance in translational studies.

At the genomic level, RNA sequencing and microarray studies of skin and peripheral blood samples from patients with SSc have identified a differential gene expression profile compared to healthy controls that changes with treatment response.[20] However, implementation of gene testing is currently hampered by high cost, with insufficient economies of scale in rare diseases.[20]

In summary, we suggest that a molecular-based classification of SSc is more robust than the conventional skin-based phenotypic model. Further research is needed to develop a futuristic model of SSc classification that is guided by comprehensive personalized clinical and molecular datapoints.

CONTRIBUTIONS

IKSN: writing – original draft, conceptualization; DMC, AAS: writing – review & editing; JWWL: writing – review & editing, supervision, conceptualization.

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