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EDITORIAL

Scleroderma: Bringing a Disease From Black-and-White Into Technicolor

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The name "scleroderma" encompasses subtypes of a systemic disease (systemic sclerosis) that are linked together by common clinical and pathologic features: skin thickening, Raynaud's phenomenon, major organ failure with evidence of autoimmunity, tissue fibrosis, and a unique noninflammatory multisystem vasculopathy. A challenge in managing scleroderma is defining as early as possible the individual patient's disease course, both to predict clinical outcomes and to determine appropriate intervention. Recognizing that subtypes exist has led to various efforts to classify scleroderma into unique subgroups that might follow a similar and predictable clinical course. The modern classification of scleroderma represents 150 years of accumulated investigation into patients with varying degrees of characteristic skin thickening and a panoply of major organ dysfunction (1). This effort has resulted in an oversimplified classification into 2 subsets based on the extent of skin involvement alone.

For the first century of its history, investigators largely divided the systemic disease into either acrosclerosis or progressive systemic sclerosis. Acrosclerosis was characterized by sclerodactyly alone, Raynaud's phenomenon, a female predominance, and usually, a nonprogressive course, whereas progressive systemic sclerosis was characterized by prominent truncal skin involvement, an equal sex distribution, and often, rapid skin fibrosis with progressive major organ disease. This dichotomization was further polarized by the emphasis on a stable clinical course among the subset of patients with calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasias (CREST syndrome) (2–4). The discovery in 1980 of anticentromere antibodies corresponding closely to the CREST syndrome further entrenched the utility of using the extent of skin disease as a surrogate for disease subtype (5).

This Boolean system was challenged by earlier studies that suggested limited differences in prognosis when grouped by skin extent and advocated for an alternative grouping based on rapidity of disease progression (6). However, in 1988, LeRoy and Medsger proposed a dichotomous skin-driven classification system based upon the respective presence (diffuse) or absence (limited) of nonfacial skin thickening proximal to the elbows and/or knees. To support this construct, they cited the dramatic 80% versus 30% difference in 6-year survival rates between limited and diffuse scleroderma reported at that time (7,8).

The utility of the dichotomization lay largely in the stratification across the 2 subtypes of the risk of interstitial lung disease and renal crisis, the 2 primary causes of mortality and morbidity in scleroderma; both more likely to be present and severe in the patient with diffuse cutaneous disease (9–11). Nevertheless, the binary system is clearly an arbitrary division across a continuous spectrum, as evidenced by intermediate risks of interstitial lung disease and survival seen when a third subgroup of patients with skin involvement extending proximally but excluding the trunk is considered (12,13).

The more recent discovery of antibodies associated with an increased risk of interstitial lung disease further underscores the disease heterogeneity within each skin subtype. Anti–topoisomerase I and anti–U11/U12 RNP antibodies denote an increased risk of interstitial lung disease but are seen in both limited and diffuse skin disease (14). Anti-Th/To antibodies, which associate closely with limited skin disease, also impart an increased risk of interstitial lung disease (15). Conversely, RNA polymerase III antibodies correlate with diffuse disease and a marked increase in the risk of scleroderma renal crisis but a lower risk of interstitial lung disease (16). Compared to the wide discrepancy in mortality between skin subtypes cited in the 1980s, a more recent

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cohort study demonstrated a less dramatic 10% difference in mortality at 10 years between patients with limited versus those with diffuse skin involvement, suggesting that the simplified skin system does not distinguish as ideal a separation of outcomes as once was thought (11). Focusing on skin manifestations alone clearly misses important features of the disease process, including serologic biomarkers and other organ involvement.

In this issue of *Arthritis & Rheumatology*, Patterson et al (17) use extended semiquantitative autoantibody levels to group patients into 5 shared expression patterns and show that these groupings correspond closely to shared patterns of organ involvement. The investigators' method is particularly appealing in its use of a data-driven approach to account for potential interactions among multiple circulating antibodies within an individual. They demonstrate that nearly half of the patients in this cohort expressed multiple autoantibodies. Given the suspicion that antibodies in scleroderma may themselves be pathogenic or are a unique biomarker of the underlying autoimmune disease process, this approach is intuitively more likely to account for some of the clinical heterogeneity seen among patients with a specific circulating autoantibody. While the identified clusters were defined largely by the dominant scleroderma-specific antibody expressed (namely, anti–topoisomerase I, anti–CENP-A or anti–CENP-B, and anti–RNA polymerase III), the analysis also identified 2 phenotypically distinct subgroups among patients with RNA polymerase III antibodies, based on the antibody concentration. The authors demonstrate phenotypic separation among these subgroups across most clinical outcomes examined and argue that this autoantibody-defined categorization may be more meaningful than the traditional limited or diffuse clinical nomenclature.

Patterson and colleagues' study uses a form of latent subtype identification, is quantitative, and is easily incorporated into other systems that have used clinical characteristics or a shared pattern of disease evolution. Other attempts to categorize patient subsets based on shared clinical features, rather than a predetermined decision rule, have grouped them based on changes in skin score over time (18), changes in the percent predicted forced vital capacity (19,20), or gene expression patterns in the skin (21–24). Each of these approaches has resulted in a small number of subgroups that define the range of phenotypes captured by the stratification characteristics. More importantly, each of these subgroups defined by a quantitative clinical parameter has uniquely identified patients with other disease manifestations in common, often across organ systems.

An ideal system of classification of scleroderma would group patients based on shared patterns of underlying pathogenesis, a similar pattern of organ involvement, and prognosis, and could be readily applied in the clinical setting to inform patient management. The binary system of limited or diffuse scleroderma has endured for over a century largely because of its rapid bedside assessment, its ease of application, and the concept that further subdivisions did not improve prediction of clinical outcomes. Fine clinical phenotyping, serologic studies, and now, availability of electronic medical records along with large prospectively collected cohort data have proven a major impetus to clinical implementation of longitudinal analytical measures.

The lens is shifting to a more comprehensive picture of scleroderma. The increasingly granular understanding of the myriad clinical manifestations of scleroderma, and the explosion of both quantifiable and longitudinal data available for each patient, demand a more versatile means of identifying patient subgroups. Two conceptually competing, though not necessarily exclusive, approaches are poised to replace the skin-based stratification: the deterministic approach, such as that illustrated by Patterson et al, wherein detailed characterization of antibodies and components of protein signaling pathways are used to predict clinical outcomes, and a dynamic trajectory approach, wherein patterned changes in clinical phenotype over time are exploited to infer underlying pathogenic mechanisms and future prognosis.

Further investigation into how extended serology-based and tissue-based techniques inform prognostication longitudinally, and how this interacts with clinical phenotype over time, will determine the role of these sophisticated approaches in the clinical and research settings. The black-or-white system of diffuse versus limited scleroderma will surely persist due to its simplicity and entrenched clinical terminology. However, the future of insight into scleroderma is bright and is best viewed in Technicolor.

AUTHOR CONTRIBUTIONS

Drs. Ligon and Wigley drafted the article, revised it critically for important intellectual content, and approved the final version to be published.

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