Editorial: Update on Scleroderma and Other Fibrosing Syndromes
Soumya Chatterjee

With the turn of the century, the knowledge of the pathogenesis of fibrosing disorders has revolutionized, largely because of better understanding of the molecular mechanisms of fibrosis. This section update gives us a glimpse of the recent advances in the field from internationally renowned experts in scleroderma (SSc) and other fibrosing syndromes. Considerable advancement has been made in the last 1 to 2 years in the field of fibrosis, and hence a section discussing these advances was necessary. In addition, the field of microvasculopathy associated with scleroderma also needed to be updated because important advances have been made in this field as well. Also included are updates on gastrointestinal manifestations, SSc-associated interstitial lung disease and pulmonary hypertension, as well as implications of different autoantibody subsets in SSc, and an update on accelerated atherosclerosis and macrovascular disease. Furthermore, a section on scleromyxedema, a close scleroderma mimic, but with distinct differences, was included, as readers should be acquainted with novel therapeutic updates for this rare but potentially life-threatening condition.

Castelino et al. (pp. 607–614) do a remarkable job in bringing us up to date on the regulation of fibrosis at a molecular level and introduce us to some novel targets for disrupting the fibrotic process in SSc. The authors discuss how this may be achieved by interfering with cytokine pathways, affecting the destiny of mesenchymal cells, slowing down senescence, dispelling activated myofibroblasts, and modulating the milieu of the extracellular matrix.

The fundamental role of microvascular endothelial cells (MVECs) in the pathogenesis of scleroderma is emphasized by Altorok et al. (pp. 615–620). The authors highlight the principal mechanisms of MVEC injury. In addition to initiation of scleroderma microvasculopathy, MVECs are thought to be involved in the activation of fibroblasts through certain cytokine and growth factor release, including CCN2, leading to production of a highly active population of fibroblasts. Epigenetic factors also seem to play an important role in the pathogenesis of SSc, including defective progenitor endothelial cell function. Purified subsets of antiendothelial cell antibodies, such as anti-intercellular adhesion molecule-1 antibodies, have been identified, and possible mechanisms for defective vascular endothelial growth factor signaling have been proposed as well.

Kirby et al. (pp. 621–629) provide an update on SSc-associated gastrointestinal disease. In the last few years, there has been emerging evidence supporting the association of active gastrooesophageal reflux disease and interstitial lung disease. Newer forms of therapy for Barrett's oesophagus, such as radiofrequency ablation, now provide hope of eradication of this once incurable condition. Recent studies reinforce strong associations between gastric antral vascular ectasias (watermelon stomach) and presence of RNA polymerase III antibody in a subset of patients with diffuse SSc. Additionally, readers are updated about the 'UCLA SCTX GIT 2.0 questionnaire', which is now being widely used as a validated tool for evaluation of patient-reported gastrointestinal outcomes in SSc.

Fan et al. (pp. 630–636) provide a succinct and timely update on SSc-associated interstitial lung disease, a major cause of morbidity and mortality. The understanding of its pathogenesis has improved considerably, potentially setting the stage for novel therapeutic targets. Novel biomarkers and treatments of SSc-interstitial lung disease are described. Animal models that more closely resemble human SSc and new in-vivo models are also discussed.

Dr Highland (pp. 637–645) emphasizes that SSc can be associated with one or more of the different subtypes of pulmonary hypertension that have been described in the revised version of the pulmonary hypertension classification criteria (2009).[1] In addition, it is being increasingly recognized that inflammation plays a crucial role in the pathogenesis of SSc-associated pulmonary hypertension. Improvement in awareness, evaluation, and screening...
techniques is leading to earlier detection of SSc-associated pulmonary hypertension, potentially leading to improved survival.

The realization that autoantibody subsets are important in defining clinical course, risk of particular organ system(s) involvement, and prognosis has led to their incorporation into the 2013 American College of Rheumatology/European League Against Rheumatism clinical classification criteria for SSc.[2] Dr Domsic (pp. 646–652) did an outstanding job explaining the clinical significance of different autoantibody subsets in SSc, geographic variability in their prevalence, and their correlation with somewhat unique clinical phenotypes and prognosis. She also updates us about two recently described SSc-associated autoantibodies.

The pathophysiology of accelerated atherosclerosis in SSc is still unclear. Soriano et al. (pp. 653–657) discuss the potential pathogenic mechanisms of accelerated atherosclerosis and macrovascular disease, and the indirect measures for detecting and quantifying subclinical atherosclerosis in SSc. Cardiac MRI is also described as a potential tool for early detection and characterization of SSc heart disease.

Scleromyxedema is a rare disease that shares several clinical features with scleroderma and should be considered in its differential diagnosis. However, there are important differences as well. Prognosis is variable and is based on the development of specific internal organ complications. In her extensive review, Dr Hummers (pp. 658–662) discusses the clinical phenotype, current knowledge in the pathogenesis, and the role of novel therapies for this poorly understood scleroderma mimic.

Over the years, the main difficulties that have remained in the field of SSc research and therapy have included poor understanding of the complex pathogenesis; absence of good animal models mimicking all aspects of the human disease; absence of large databases (because of the rarity of the disease); and significant heterogeneity between disease subtypes (limited and diffuse), ethnic groups, geographic regions, and different organ system involvements. Moreover, there has been absence of consensus about the specific measures of disease burden. In addition, there is considerable debate regarding the precise means to differentiate activity (which, in theory, is potentially treatable and reversible) and damage (which is cumulative and potentially irreversible). In spite of all these areas of uncertainty and controversy, the field of scleroderma research is advancing rapidly. Better understanding of the molecular mechanisms of fibrosis and endothelial dysfunction can potentially result in targeted and effective disease-modifying therapies. There is an urgent need to develop such therapies for this devastating disease, and our search must fervently continue.

References


Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.