Systemic sclerosis: Views and thoughts for the future

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Systemic sclerosis (SSc) is one of the most severe connective tissue diseases [1]. Although significant progress has been made in the understanding of its pathophysiology, much more has to be done in order to identify a treatment that would allow to obtain a disease cure. A number of new experimental models of SSc have been set up, which are detailed in this issue of the journal [2], that should help to understand the mechanisms contributing to the emergence of the disease and test new therapeutic targets. However, the treatment options that have been shown to improve sclerosis in mice eventually failed to demonstrate their efficacy in the human, as recently identified in the case of tyrosine kinase inhibitors [3]. Endothelial cell hyperactivity, increased collagen production by fibroblasts, and increased production of reactive oxygen species by both of these cells represent hallmarks of the pathogenesis of SSc. Besides, endothelial cells and fibroblasts, major effort has been done in the understanding of the pathogenic role of auto-antibodies and B cells [4], but the evidences for their contribution to the pathogenesis of the disease remains actually limited. Finally, plasmacytoid dendritic cells were recently identified as playing an important role in the pathogenesis of SSc through the secretion of CXCL4 [5]. Importantly, the ability to diagnose SSc has been improved with the definition of American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) classification criteria [6], allowing to improve sensitivity and specificity as compared to the 1980 ACR criteria [7]. This new classification is based on a scoring system, a score of nine allowing to define SSc. Interestingly, these criteria include, as in the previous 1980 classification criteria [7] sclerosis proximal to the metacarpophalangeal joint as sufficient to make the diagnosis of SSc, with a score of nine. If sclerosis proximal to the metacarpophalangeal joint is not present, seven other parameters quoted 2 to 4 are to be considered including digital involvement with puffy fingers or sclerodactyly, digital ulcers or pitting scars, Raynaud’s phenomenon, telangiectasia, lung involvement including interstitial lung disease and pulmonary arterial hypertension (PAH), capillaroscopic abnormalities and autoantibodies specific for scleroderma. Interestingly, for the first time, puffy fingers and PAH are taken into account for the diagnosis of SSc [6]. The prognosis of SSc remains poor, mainly due to visceral involvement that may occur during the disease course. Most of these severe complications will be detailed in this issue of the Quarterly Medical Review, including PAH [8], interstitial lung disease [9], gastrointestinal tract involvement [10], and scleroderma renal crisis [11]. Interstitial lung disease and PAH are actually the two
major causes of scleroderma-associated deaths in patients with SSc. Gashoua MA et al. in this issue of the Quarterly Medical Journal [8] reviewed data from the literature on scleroderma-associated PAH (SSc-PAH). Despite advances in treatment options for PAH, long-term prognosis remains poor for SSc-PAH. Early detection of PAH is probably one of the key issues and in this setting. Recently, the Detect study group conducted a screening study undertaking systematically right heart catheterism in a large cohort of SSc patients for diagnosis of PAH, and proposed an algorithm using simple clinical data and non-invasive tests allowing early identification of PAH in a mildly symptomatic population [12]. Interstitial lung disease in SSc (SSc-ILD) is now the major cause of death in SSc, due to respiratory failure or fatal pulmonary hypertension. Wells et al. propose an extensive review article structuring the clinical section as a series of questions that matter in this setting [9]. Currently, the management of SSc-ILD is largely confined to immunomodulation. Treatment options in this setting are reviewed with development of future perspectives.

In order to deal with these two severe respiratory manifestations, lung transplantation is actually an option in these SSc patients. In this issue of this review, you will also find the recommendations of a French collaborative group for lung or heart-lung transplantation in patients with SSc [13], proposing an adaptation of the pre-transplant assessment to SSc and optimizing SSc patient management before, during and after surgery. Indications and contraindications for transplantation have to be adapted to the specificities of SSc. These recommendations will probably contribute to improve short- and long-term prognosis in these patients.

Scleroderma renal crisis, as reviewed by Steen et al. in this issue of the journal [11], is actually a rare manifestation of SSc but remains an important cause of death in SSc, with an overall mortality of 18 to 36% at one year [14]. Early detection of this manifestation that occur mainly in patients with early diffuse SSc and anti-RNA polymerase III antibodies remains a majors issue, allowing the early initiation of angiotensin converting enzyme inhibitors (ACEI) [11].

Among others, gastrointestinal tract manifestations are difficult to manage in patients with SSc, and a precise identification of the segment of the gastrointestinal tract involved is necessary in order to provide the adapted treatment, as reviewed by Savarino E et al. [10].

Finally, SSc is also frequently responsible for musculoskeletal manifestations. These manifestations are life-threatening in most of the cases but are responsible for pain, discomfort and disability on the long term. These manifestations are extensively reviewed by Loránd et al. [15].

Overall, we hope that this issue of the Quarterly Medical Review will provide you with up to date cutting edge information on SSc. We hope that the years to come will contribute through multicenter studies and collaborative databases to increase our understanding of this disease and improve the prognosis of our patients.

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References