Editorial paper

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Late-onset systemic sclerosis: current concepts, uncertainties, and future practice guidelines

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Systemic sclerosis (SS) is an autoimmune disease characterized by immune dysfunction, fibrosis of the skin, vascular affections, and multiple organ system dysfunctions [1]. Although SS predominantly manifests in women of reproductive age, it may present in both women and men at any period of life. With increasing life expectancy and steady population growth, the proportion of older patients with SS and other autoimmune diseases is also rising. In this context, the onset of SS in subjects above 60 years is frequently encountered.

Clinical features of SS may differ across age groups, with aging processes substantially confounding disease manifestations. In the seminal work on SS etiology and pathogenesis, published in 1963, aging was distinguished as the key pathophysiological factor [2]. Over the past six decades, no globally acceptable definitions, age thresholds, classification and diagnostic criteria, or management strategies of late-onset SS (LOSS) have been proposed. The scale of the issue has been further confounded by the growing number of LOSS patients, constituting 8–21% of all SS patients [3].

Autoimmune rheumatic diseases with late onset (above 60 years) are increasingly relevant due to global population aging and rising life expectancy trends. Aging modifies immune function, connective tissue repair, and drug metabolism [4], all of which can influence SS manifestations and efficiency of drug therapies. Immune aging, or immunosenescence, variably influences pathophysiological mechanisms in autoimmune diseases [5]. The specifics of late-onset rheumatoid arthritis (LORA) and late-onset systemic lupus erythematosus (LOSLE) have been explored in several recent reports [6, 7]. By contrast, the evidence in the field of LOSS is based on scarce reports and overviews, possibly reflecting its relatively rare occurrence compared with LORA and LOSLE. Subsequently, LOSS clinical phenotypes and outcomes remain insufficiently elucidated.

Arguably, autoimmune mechanisms, clinical features, and outcomes in LOSS early-onset systemic sclerosis (EOSS) differ substantially [8]. Higher frequency of heart involvement, lower incidence of digital ischemia and ulcers, and higher incidence of pulmonary hypertension are characteristic for LOSS. Moreover, limited SS, rather than diffuse SS, is more common in LOSS than in EOSS. In LOSS, anticentromere antibodies are more common than SCL-70 antibodies [9]. Like in LORA and LOSLE, LOSS is associated with numerous comorbidities [3, 8, 9]. Comorbid status, multimorbidity, and health professionals' unawareness of the specifics of SS onset in individuals above 60 years may complicate diagnostic workflows and result in diagnostic delays, which are also frequent in other autoimmune rheumatic diseases.

Presumably, primary health specialists are inadequately informed of the incidence of LOSS and may not suspect SS onset in older subjects. Manifestations such as skin hardening, induration, hyperpigmentation, and telangiectasia may be interpreted by health professionals as normal signs of aging, delaying LOSS diagnosis. Likewise, initial gastrointestinal, pulmonary, and cardiac manifestations in LOSS can be confused with normal aging conditions. Notably, Gerald P Rodnan, the founder of SS studies, noted diagnostic challenges in older age subjects as early as 1962, when he reported two patients aged 69 and 70 with "progressive systemic sclerosis" [10].

Diagnostic delays in LOSS likely result in a narrow window of opportunity and low efficiency of drug therapies. The treat-to-target strategy, often involving maximally tolerable drug doses and polypharmacy, is particularly challenging in aging subjects. As a result, a comorbid and multimorbid background in LOSS patients may contribute to greater mortality rates.

The definition of late-onset systemic sclerosis faces two conceptual challenges: distinguishing late vs. elderly-onset systemic sclerosis, and determining the age

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threshold. The terms "late-onset systemic sclerosis" and "elderly-onset systemic sclerosis" are often used interchangeably in the current literature [11]. However, terms referring to "elderly" are considered inappropriate in view of concerns regarding ageism [12]. The age threshold in the context of LOSS is still variably reported, ranging from 50 to 75 years. Most studies identify 60 and 65 years as diagnostically important age cutoff points. Such uncertainty in disease definitions confounds reliable statistical reporting and evidence synthesis in the field. Currently, using 60 years as a critically important age of LOSS patients is in line with the World Health Organization's approach to life periods [13]. Accordingly, the following definition can be proposed for approval of the global rheumatology community: **"Late-onset systemic sclerosis (LOSS) is a clinical phenotype of systemic sclerosis with disease onset at age 60 years or older".**

To sum up, future studies of emerging concepts and strategies in the field of SS should rely more on published expert opinion syntheses and global rheumatology discussion forums. The same is equally applicable to other autoimmune rheumatic diseases with variable definitions and geriatric strategies [14]. Late-onset systemic sclerosis practice guidelines, like those on LORA and LOSLE, require tailored approaches [15]. The first guidelines on LORA were developed in Japan [16], which is unsurprising, as Japan has one of the highest life expectancies in the world. Moving forward, LOSLE and LOSS guidelines may also be developed in the near future by rheumatology and geriatrics experts.

Key points

1. Late-onset systemic sclerosis (LOSS) is a clinical phenotype of systemic sclerosis with disease onset at age 60 years or older.
2. Steady population growth and increased life expectancy can lead to an increase in the incidence of LOSS.
3. Immunological features, comorbidities, and outcomes distinguish LOSS from other SS clinical phenotypes.
4. Normal aging processes, comorbidities, and health professionals' unawareness may be confounders of diagnostic delays in LOSS.
5. Late-onset systemic sclerosis practice guidelines are increasingly needed.

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