Systemic Scleroderma

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Systemic scleroderma (SSc, progressive systemic sclerosis) is a generalized connective tissue disease which clinically manifests itself by thickening – fibrosis – and cutaneous sclerosis of various extents (scleroderma) and a typical involvement of multiple internal organs [1]. At the same time, there occur fibrotic and sclerotic changes in vascular walls, disturbances of microvascularization, and disorders of humoral and cellular immunity. It affects 3–8 times more women than men. It develops usually in middle age, with an annual incidence of about 3 – 19 new cases per million population. One of the major clinical manifestations is Raynaud's phenomenon with trophic changes, skin induration, and involvement of gastrointestinal tract, lungs, heart, and kidneys [2].

The patients with late-onset SSc, may exhibit visceral pathology in the earlier stages of the disease, as documented by the study published by Volkov et al. [3]. The authors compared clinical manifestations in patients under and over the age of 50 and gender-dependent changes. Late-onset SSc patients developed SSc visceral manifestations in the first 3 years of the disease. Men with late-onset SSc had predominantly the diffuse cutaneous form of the disease with progressive skin involvement and induration and significant microcirculation changes. In contrast, the study by Hügle et al. [4] comparing SSc patients under and over 75 years demonstrated that the patients over the age of 75 had more frequently limited than diffuse SSc.

Myalgia, arthralgia, and arthritis are nonspecific symptoms in SSc, while tendon friction rubs at finger flexors are thought to be diagnostic of SSc. Late-onset SSc patients had a more marked muscle weakness [5]. Peripheral trophic changes are relatively less frequent in late-onset SSc than in early-onset SSc.

Fibrotic changes in the digestive tract result in retardation or arrest of the passage of the intestinal contents and dilatation of the distal esophagus. This is manifested by dysphagia, pyrosis, gagging, abdominal pain or even colic, sometimes malabsorption and emptying disorders, constipation in particular. These symptoms are usually accentuated in late-onset SSc patients.

Pulmonary involvement occurs in the form of interstitial lung disease or pulmonary arterial hypertension. A more frequent form is alveolitis with the subsequent interstitial fibrosis. Frequency of the interstitial process probably increases with age and often leads to secondary pulmonary hypertension. However, the study by Hügle [4] proved this difference neither by radiographic methods nor by function tests.

Primary pulmonary hypertension without interstitial lung disease is according to the American authors twice as frequent in late-onset SSc with the beginning of the disease after the

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age of 60 [6]. Similarly, the study by Manno [5] showed a higher risk of pulmonary hypertension in late-onset SSc patients. Cumulative incidence during 5 years was higher in the late-onset SSc group (9 %) as compared to early-onset SSc patients (2.7 %; $p<0.001$) [7]. The study by Hügle [4] also revealed in the group of patients over the age of 75 a more prevalent pulmonary hypertension (measured by echocardiography) as well as systemic hypertension and diastolic dysfunction.

Cardiac involvement may have several forms, e.g., a frequent finding of often asymptomatic pericarditis. Myocardial involvement is manifested in the conductive system by abnormal heart rhythm and atrioventricular blocks. These findings are more frequent and more serious in late-onset SSc [3], which was confirmed by the study published by Manno [5].

Renal manifestation is reported in 8–10 % of patients. The most severe form is scleroderma renal crisis with abrupt onset of hypertension and rapid development of oliguria or even anuria. A higher frequency of renal manifestation has been documented also in an American cohort study [5].

The laboratory findings usually include a mild normochromic normocytic anemia and thrombocytopenia. Acute phase reactants values are often slightly elevated or normal and thus do not reflect the disease activity. Immunological tests show the presence of rheumatoid factors and cryoglobulins in up to 40 % of patients. Antinuclear antibodies are positive in up to 90 % of cases, usually with granular immunofluorescence pattern. A more specific anticentromere antibody test is positive in about 70 % of patients with limited cutaneous SSc [8]. The study published by Manno evaluated 2,300 SSc patients and showed that incidence of anticentromere autoantibodies was considerably higher in patients older than 65 years as compared to younger individuals (42 % vs. 27 %; $p=0.001$) (Table 6.1). This was confirmed also by a large cohort study based on the EUSTAR/EULAR database [4]. In contrast, anti-DNA topoisomerase I antibodies (anti-Scl-70) are found in up to 40 % of patients with the diffuse cutaneous form.

Table 6.1 Clinical symptoms and laboratory findings in systemic scleroderma with younger- versus late-age onset

Manifestation	SSc, younger-age onset	SSc
Anticentromere antibodies (ACA)	Positive mainly in limited cutaneous form	In general higher incidence
Pulmonary hypertension, muscle weakness, involvement of the heart and kidneys	More frequently in diffuse cutaneous SSc	In general higher incidence
Peripheral vasculopathy	Frequent	Less frequent
General prognosis	Better	Markedly worse

Modified according to Manno et al. [5] and Hügle et al. [4]

Prognosis of the disease is usually given by severity of pulmonary involvement; the interstitial process usually gradually leads to development of global respiratory insufficiency with fatal consequences. Pulmonary arterial hypertension, on the other hand, is characterized by rapid progress with a very poor diagnosis. The age over 75 years is in late-onset SSc associated with a substantially worse prognosis than in patients older than 60 years [9]. In the cohort from the EUSTAR/EULAR database, mortality due to SSc was higher in the late-onset group, but the survival time from diagnosis was longer compared with the younger patients. The disease is manifested by a far more severe involvement of individual organs, and the condition is often complicated by various comorbidities; therefore, diagnosis must be established as soon as possible. In the patients, special attention should be paid to the incidence of malignant processes, including solid tumors in men with extensive skin involvement; pulmonary fibrosis as a predisposition to lung cancer, breast cancer in women, and chronic reflux esophagitis; and Barrett's esophagus as a predisposition to esophageal carcinoma.

SSc treatment must be always comprehensive. The basic process cannot be usually controlled by pharmacological treatment as the effect of most preparations can be observed only in the cutaneous form of the disease. In the edematous phase of the disease, patients receive corticosteroids

with methotrexate and in active alveolitis corticosteroids on a long-term basis and repeated intravenous pulses of cyclophosphamide [10]. Other procedures are organ specific and have only a symptomatic effect. In late-onset SSc treatment, the basic therapeutic procedures do not differ substantially from treatment of younger patients, only it is complicated by frequent visceral organ involvement and neurological comorbidities and the associated risk of serious drug interactions. The future of a complex SSc treatment lies in biological preparations that will be targeted at individual phases of the immunopathological process. The results of clinical trials focused on the current biologic drugs used to treat rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis are not unequivocal.

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