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Review

Systemic sclerosis evolution of disease pathomorphosis and survival. Our experience on Italian patients' population and review of the literature

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ABSTRACT

The clinical spectrum and prognosis of systemic sclerosis (SSc) seem to vary among patients' populations recruited during different time periods. In order to verify this possible evolution we investigated the clinico-serological and survival rate in a large Italian SSc series (821 patients; 746 females, 75 males; mean age 53.7 ± 13.9 SD years) recruited between 2000 and 2011. The observed findings were compared with previous studies of the world literature.Compared to older Italian SSc series, the present patients' population showed a significantly increased prevalence of limited cutaneous SSc (from 72 to 87.5%; $p \leq .0001$) and serum anti-centromere antibodies (from 39 to 47,4%; $p \leq .001$), with a significant reduction of lung (from 81 to 63.7%; $p \leq .0001$), heart (from 35 to 20.5%; $p \leq .0001$), and renal involvement (from 10 to 3.8%; $p \leq .0001$), and skin ulcers (from 54 to 16.5%; $p \leq .0001$). Cumulative 10th-year survival showed a clear-cut increase (80.7%) compared to our previous series (69.2%). These findings were mirrored by the results of survival studies published during the last five decades, grouped according to the time periods of patients'' recruitment at the referral centers. A clear progression of 10th-year survival rates was detectable, from the 54% median survival of the oldest studies (1935–1974) to 74% and 83.5% of the more recent SSc series, 1976–1999 and after 1999, respectively. In conclusion, the favorable evolution of SSc pathomorphosis and prognosis during the last decades might be related to more diffuse physician/patient awareness of this harmful disease and availability of diagnostic tools, the consequent wider recruitment of patients in the early stages of the disease, as well as to the improved therapeutic strategies.

Contents

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1. Introduction

Systemic sclerosis (SSc) is a connective tissue disease characterized by endothelial dysfunction, dysregulation of fibroblasts with collagen overproduction, and complex immune system abnormalities [1–3]. A frequent consequence of this chronic disease is the multiple organ damage/failure responsible for marked impairment of the patient's quality of life and increased mortality [4–9]. Since the sixties an increasing number of clinical studies evaluated the impact of the main SSc manifestations on the disease prognosis as well the cumulative SSc survival [4,5,10–45]. In our previous study we underlined the progressive improvement of the mean cumulative SSc 10th-year survival as emerging from the studies published during the nineties if compared to previous reports present in the literature [5]. This observation was hypothetically related to both different compositions of scleroderma patients' series recruited during the last years and improved SSc patients' management. In order to verify this hypothesis we further investigated the composition of SSc clinical features and the cumulative 10th-year survival in a large Italian series recruited between 2000 and 2011 and compared the observed findings to that reported in our previous study [5]. In addition, we systematically reviewed the world literature on this topic; the updated findings were carefully analyzed with particular attention to the possible evolution of the SSc pathomorphosis and prognosis during the last decades.

1.1. Patients and methods

The present study involved 3 Italian university-based divisions of rheumatology (University of Modena, University of Ferrara, and 2nd University of Napoli) with comparable, long-term experience in SSc patient management.

1.1.1. Patients

The study population was recruited between 2000 and 2011 at the 3 participating centers. Eight hundred twenty-one patients (746 females, 75 males; mean age at presentation, 53.7 ± 13.9 SD years) were included in the study (Table 1).

At the beginning of the follow-up, corresponding to the time of diagnosis, all patients fulfilled the 1980 American College of Rheumatology (formerly ARA) criteria for SSc classification. In all cases the diagnosis of SSc was done by an expert rheumatologist on the basis of a wider panel of clinical, serological, and capillaroscopic parameters, as previously proposed [5,46–50].

At the same time, patients were also classified based on the extent of skin sclerosis as limited cutaneous scleroderma (lcSSc: sclerosis of distal extremities, not above the elbow and knees, with or without sclerosis of neck and face) and diffuse cutaneous scleroderma (dcSSc: sclerosis of both distal and proximal extremities, with or without truncal involvement) [5].

1.1.2. Clinical assessment

Standardized criteria were followed for the evaluation of clinico-epidemiological parameters. In particular, the patient's age was evaluated at the following conventional times: a) at the appearance of isolated Raynaud's phenomenon; b) at the disease onset, considered to be the age at which the first non-Raynaud's sign(s) and/or symptom(s) compatible with the disease appeared, i.e. digital ischemic lesions, puffy hands, sclerodactyly with or without proximal scleroderma, dyspnea, and/or dysphagia; c) at the SSc diagnosis at the referral centers [5].

Organ involvement was evaluated according to the criteria previously described [2,4,5,49,50]. In particular, each type of involvement was defined as follows: 1) peripheral vascular: Raynaud's phenomenon with digital pitting and/or ulcerations or gangrene; 2) joint: presence of polyarthralgia or arthritis when inflammatory changes were observed in more than 2 joints; 3) muscle: isolated muscle weakness or weakness associated with elevated serum creatine kinase with or without electromyographic or histologic changes of inflammatory myopathy; 4) esophageal: dysphagia and/or esophageal radio-graphic dysmotility; 5) pulmonary: bibasilar fibrosis at high resolution computerized tomography and/or restrictive lung disease on pulmonary function tests, including diffusion capacity for carbon monoxide (DLCO); 6) cardiac: at least 1 of the following symptoms: pericarditis, congestive heart failure, severe arrhythmias, and/or atrioventricular conduction abnormalities; 7) systolic pulmonary arterial pressure (sPAP) calculated by means of B-mode Doppler echocardiography in order to detect patients with possible pulmonary arterial hypertension (sPAP >40 mm Hg); and 8) renal: scleroderma renal crisis with increased diastolic blood pressure and/or progressive renal failure.

The presence of serum autoantibodies was investigated by means of standard techniques [4,5,39,41–53]: antinuclear (ANA), anti-centromere (ACA) and anti-nucleolar antibodies (ANoA) by indirect immunofluorescence on Hep-2 cell lines (dilution 1:40); anti-extractable nuclear antigen (ENA) antibodies, including anti-Scl70, -Sm, -RNP, -SSA/SSB.

Table 1
Clinico-epidemiologic features of 821 Italian patients with SSc[a].

	Beginning of follow-up	End of follow-up	p value
Number of patients	821	686	–
Deceased patients	–	9.1	–
Patients lost to follow-up	–	7.3	–
Female/Male ratio	9.9/1	12/1	NS
Mean age (year)	53.7 ± 13.9	58.3 ± 14.2	–
Mean disease duration (year)[b]	9.2 ± 10.3	14.7 ± 10.8	–
Mean disease duration (year)[c]	3.6 ± 5.4	8.1 ± 5.9	–
Mean follow-up (year)	0	4.5 ± 3.2	–
Cutaneous subsets L/D	87.5/12.5	89/11	NS
Hypermelanosis	17.1	24.4	.005
Calcinosis	9.8	13.7	NS
Teleangectasias	48.3	55.7	NS
Skin ulcers	22.6	16.5	.002
Raynaud phenomenon	93.5	91.2	NS
Sicca syndrome	40.7	47	.039
Arthralgias	36.9	35.8	NS
Arthritis	4.6	5.5	NS
Myositis	3.5	3.4	NS
Dysphagia	41	43.4	NS
Dyspnea	36.8	42	.04
Lung involvement	55.6	63.7	.001
Heart involvement	15.1	20.5	.001
Renal involvement	2	3.8	.04

SSc = systemic sclerosis, NS = not significant.
[a] Except where otherwise indicated, values are percentages.
[b] From Raynaud's onset.
[c] From SSc onset.

1.1.3. Survival rates

At the end of the study the vital status of all patients' lost to follow-up was established by contacting the patients themselves or relatives, their primary care physician, or the municipal death registry. For patients known to have died, hospital records, autopsy reports, or death certificates were examined, when possible, to establish the date and cause of death. On the whole, 92.7% of patient accountability was determined at the end of the study.

Causes of death were classified as definitely SSc-related (organ insufficiency, such as renal crisis, or by a manifestation attributable to no other causes or predisposing factor than SSc, for example severe lung fibrosis), possibly SSc-related (manifestation either aggravated by SSc-related organ involvement, such as pneumonia complicating severe lung fibrosis, or occurring with increased frequency in SSc, for example lung cancer), and unrelated to SSc organ injury or treatment.

1.1.4. Statistical analysis

Cumulative survival rates were computed by the Kaplan–Meier method [54,55], and the difference between survival curves by the