Patients with systemic sclerosis associating other autoimmune diseases have a milder disease course

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ABSTRACT

Background and objectives. Systemic sclerosis (SSc) is a multisystem connective tissue disease (CTD), being one of the most heterogeneous diseases of the spectrum of CTDs. It may associate other autoimmune diseases (AIDs), therefore in this study we aimed to evaluate the prevalence of other AIDs in a cohort of patients with SSc and to evaluate their prognosis in comparison to patients with SSc without this association.
Patients and methods. We performed a retrospective study in patients with SSc satisfying the ACR 1980 or the ACR/EULAR 2013 criteria, who were evaluated between January 2005 and May 2014 in our SSc center. These patients were investigated according to the EUSTAR recommendations, including modified Rodnan Skin Score (mRSS), lung function tests (LFT), echocardiography etc. As a control group for evaluating the prevalence of the AIDs we used all patients with Rheumatoid Arthritis (RA) visiting our clinic between January-December 2005. Data of all RA patients were collected from the electronic database of the hospital. All AIDs mentioned in the discharge diagnoses were recorded. Between-group comparisons were made with the chi-square test for nominal variables and with the independent-sample t-test for numeric variables.
Results. 144 patients with SSc were included: 88.8% females, 66.6% with the limited cutaneous subset of disease (lcSSc), mean age 53.9 ± 12.8 years, mean disease duration at study enrollment 5.1 ± 10.5 years and a mean follow-up time of 3.7 ± 2.6 years. Prevalence of the AID in the SSc cohort was 19.4%, patients with lcSSc being more prone to associate other AID ($p = 0.001$). We noted a tendency towards less interstitial lung disease ($p = 0.056$) and less digital ulcers ($p = 0.081$) in patients with SSc and AIDs. Comparing skin involvement for each year of follow-up in patients with SSc with and without and AIDs we observed that the first tended to have lower and more stable values of the mRSS.
Conclusion. Patients with SSc and AIDs tend to have a better outcome than the ones without this association. mRSS remains stable across the years in patients with SSc and AID, with lower values than the SSc patients.

Keywords: systemic sclerosis, autoimmune disease, polyautoimmunity

Systemic sclerosis (SSc) is a chronic, multisystem disorder associated with the highest mortality among the connective tissue diseases (CTDs) (1). Being not only the prototype of fibrotic diseases but also an autoimmune and vascular disease, SSc is a heterogeneous condition with variable clinical presentations and course, frequently associating other autoimmune conditions – which makes the management of these patients more difficult.

Despite all efforts to understand the pathogenesis of SSc, some pieces of the puzzle are still missing. In the last years, studies brought into light evidence that SSc shares a genetic background with other au-

toimmune diseases (AID) and certain genes can predispose to multiple AIDs (2). It has long been known that SSc can be associated with other autoimmune rheumatologic diseases ("overlap syndromes") and also with other autoimmune conditions, but the prevalence of these associations in SSc is still a matter of debate.

In this study we included under the name of AIDs any other connective tissue diseases except SSc, and also antiphospholipid antibody syndrome, rheumatoid arthritis, autoimmune thyroiditis, autoimmune hepatitis, primary biliary cirrhosis and type I diabetes mellitus (3). A disease is regarded as an autoim-

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mune disease when it meets the Witebsky's postulates (direct evidence from transfer of pathogenic antibody or pathogenic T cells, indirect evidence based on reproduction of the immune disease in experimental animals and circumstantial evidence from clinical clues) (4).

The aim of our study is to determine the prevalence of AIDs in the cohort of patients with SSc of the EUSTAR center 100 and to compare the outcome of these patients with the ones without an associated AID.

PATIENTS AND METHODS

We performed a retrospective study by reviewing the charts of all SSc patients, diagnosed according to ACR 1980 criteria or the ACR/EULAR 2013, who were evaluated between January 2005 and May 2014 in the EUSTAR center 100 (Dr. Ion Cantacuzino Clinical Hospital, Bucharest, Romania), with regard to the association of another AID. Patients were investigated yearly according to the EUSTAR recommendations, including the modified Rodnan Skin Score (mRSS), blood tests, lung function tests (LFT), echocardiography, chest x-Ray etc. All SSc patients have given written informed consent for participation in the EUSTAR database and in any observational study conducted on EUSTAR data. We registered any diagnosis of one of the following diseases: Rheumatoid Arthritis (RA), Systemic Lupus Erythematosus (SLE), Sjögren's Syndrome (SS), Dermatomyositis (DM), Polymyositis (PM), Autoimmune Thyroiditis (AIT), Primary Biliary Cirrhosis (PBC), Type 1 Diabetes Mellitus (Type 1 DM), antiphospholipid syndrome (APLS). Diagnosis of the associated disease was made according to the expert opinion. As a control group for evaluating the prevalence of AIDs we used all patients with Rheumatoid Arthritis (RA) visiting during the year 2005 the rheumatology clinic of the same hospital, followed-up until May 2014. Patients diagnosed with both SSc and RA were analyzed in the SSc group. We compared the patients with SSc to the ones with RA regarding the prevalence of AIDs. We also compared the SSc patients associating any AIDs to SSc patients without AIDs in regard to mortality, pulmonary function tests, and vascular impairment, aiming to determinate the prognosis of these patients. Data on AIDs of SSc patients and all data of RA patients were collected from the electronic database of the hospital. The study was approved by the local ethics committee. The statistical analysis was performed using the IBM SPSS 20.0 software. Between-group comparisons were made with the chi-square test for nominal variables and with the independent-sample t-test for numeric variables. A p-value below 0.05 was considered statistically significant.

RESULTS

We included 144 patients with SSc, among which 88.8% females, and 66.6% with limited cutaneous SSc (lcSSc). The control group included 511 patients with RA. Demographic data of the SSc and RA patients are presented in Table 1.

TABLE 1. Demographic data of the patients with SSc and the control patients with RA

	SSc patients (n = 144)	RA (n = 511)
Age at inclusion, years (mean ± SD)	54.3 ± 12.3	61,6 ± 13.2
Age at diagnosis, years (mean ± SD)	47.76 ± 12.91	49. ± 14.9
Disease duration, years (mean ± SD)	6.5 ± 6.4	12.6 ± 9.3
Female gender	128 (88.9%)	419 (82.0%)
Deceased before May 2014	14 (9.7%)	6 (1.2%)

Prevalence of AIDs in the SSc cohort

The overall prevalence of AIDs inSSc patients was 19.4%, with RA being the most frequent association, followed by SLE (5.6%) and AIT (4.9%) (Table 2). In the RA group the overall prevalence of AIDs was only 4.7%, SS (2.3%) and AIT (1.8%) being the most frequent associations (Table 2). We also

TABLE 2. Prevalence of associated autoimmune diseases (AIDs) in SSc patients and in the RA control cohort

	SSc patients (n = 144)	PR patients (n = 511)	P value
Any associated AID	19.4% (n=28)	4.7% (n=24)	<0,001
Rheumatoid Arhritis	11.1% (n=16)	–	–
Systemic Lupus Erythematosus	5.6% (n=8)	0.4% (n=2)	<0.001
Autoimmune Thyroidis	4.9% (n=7)	1.8% (n=9)	0.059
Sjögren's Syndrome	4.2% (n=6)	2.3% (n=12)	NS
Dermatomyositis/ polymyositis	2.1% (n=3)	0	0.01
Primary Biliary Cirrhosis	0.7% (n=1)	0	NS
Type 1 Diabetes mellitus	0.7% (n=1)	0	NS
Antiphospholipid Syndrome	0.7% (n=1)	0.2% (n=1)	NS

registered 6.9% (n = 10) SSc patients associating two AIDs, and 2 SSc patients presented more than two AIDs (3 and 4 AIDs, respectively). The most prevalent associations with SSc were SLE + SS, RA + AIT, or RA + SLE. There was only one patient in the RA cohort associating 2 other AIDs.

Characteristics of patients with SSc and AID

There were no significant differences regarding the demographic data between patients with SSc associating AID and patients with RA associating AID (Table 3). Patients with lcSSc tended to associate more frequently other AIDs than patients with diffuse cutaneous SSc (dcSSc).

TABLE 3. *Demographic characteristics of patients with SSc with and without associated autoimmune disease (AID)*

	SSc+AID (n = 28)	SSc, no other AID (n = 144)	p value
Age at inclusion, years (mean ± SD)	56.8±10.5	54.3±12.3	NS
Age at diagnosis, years (mean ± SD)	49.58 ± 12.9	47.76±12.91	NS
Disease duration, years (mean ± SD)	7.2 ± 6.1	6.5±6.4	NS
Female gender	100%	88.9%	NS
lcSSc	85.71%	48.7%	0,001
Survival rate	92.8%	89.7%	NS
Initial symptom – Raynaud's Phenomenon	75%	81.9%	NS

As expected, SSc patients with other AIDs presented more frequently musculoskeletal involvement and *sicca* symptoms in comparison with SSc patients without AIDs: arthritis (29.6% vs. 18.3%, p = 0.18), arthralgiae (71.4% vs. 59.5%, p = 0.24), muscle weakness (32.1% vs. 26.5%, p = 0.55), xerostomy (32.0% vs. 26.9%, p = 0.6), xerophtalmia (36% vs. 11%, p = 0.005), however except for xerophtalmia these did not reach statistical significance.

Outcomes of SSc patients with AIDs

Despite the fact that we did not obtain statistically significant correlations, we observed a trend to a better outcome regarding the cardiac, vascular and pulmonary involvement in patients with SSc and associated AIDs. We also recorded less deaths in patients with SSc and AIDs (7.1% vs. 10.3%). Clinical parameters associated with a poor outcome like calcinosis, tendon friction rubs, hipo/hyperpigmentation and telangiectasiae are analyzed in Table 4.

TABLE 4. *Outcomes of patients with SSc and associated AIDs, compared to patients who have only SSc*

	SSc with AIDs (n = 28)	SSc (n = 116)
Deceased patients	7.1%	10.3%
Palpitation	25%	52.2%
Cardiac conduction abnormalities	11.1%	21.2%
Arrythmia	7.1%	9.6%
Forced Vital Capacity < 80%	13%	30.9%
Diffusing capacity of the lung for carbon monoxide < 75%	69.6%	78.7%
Digital Ulcers	10.7%	26.7%
Digital pitting scars	42.9%	54.3%
Tendon friction rubs	0%	11.3%
Calcinosis	21.4%	27.2%
Telangiectasiae	59.3%	66.1%
Hipo/Hyperpigmentation	50%	60%

Skin involvement in SSc patients with AIDs

Dividing the SSc patients without AIDs in the two LeRoy disease subsets (dcSSc and lcSSc) and comparing the mRSS with the SSc patients with AIDs we noticed that in SSc + AIDs patients, as well as in patients with lcSSc, mRSS remains rather stable during the disease course, while in dcSSc the value of mRSS decreases in time. The mean value of the yearly mRSS was lower in the patients SSc with AIDs (Figure 1).
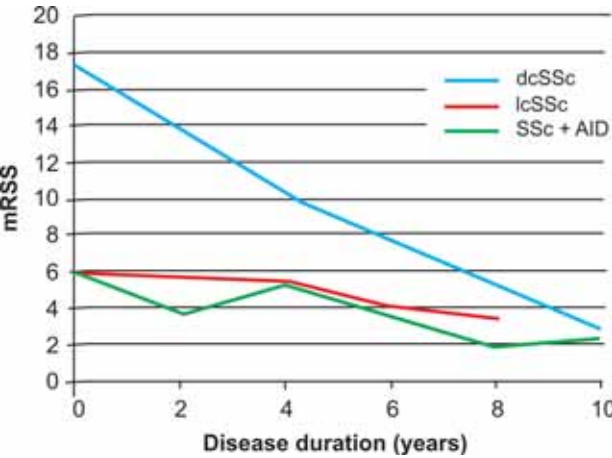

FIGURE 1. *Evolution of mean subgroup mRSS during the follow up of patients with SSc and AIDs in comparison with patients with (only) lcSSc or dcSSc*

DISCUSSION

We have shown in our study that patients with SSc can associate more frequently other AIDs, not only in comparison to general population, but also to patients with RA. The exact prevalence of the associated AIDs is still a matter of debate. Different studies show a varying prevalence of AID from 11% to

40% (5). A recent meta-analysis concluded that the prevalence of AID in SSc patients is 26% (6), with AIT being the most prevalent (10,4%), followed by SS (7,7%) and DM/PM (5,6%). The prevalence of AID in our cohort was lower, rising the suspicion of underdiagnosed patients. Comparing the prevalence of AIDs in SSc patients with the one in RA control cohort and in the general population (3-6%) (7) we found that frequency of AIDs is almost 4 times higher in SSc patients. Our study assigns RA as the most frequent association in SSc patients. We do not exclude the possibility of an overestimated number of RA patients due to severity of the musculoskeletal involvement that sometimes is difficult to classify. When applying the 2010 Criteria for Rheumatoid Arthritis on the SSc patients they were satisfied by less than 50% of patients. But the new classification criteria for RA are designed for identifying the subset of patients who are presenting with an unexplained inflammatory arthritis of a peripheral joint, so they should not be used in patients with other well established conditions (8). Patients with SSc should be regarded as a special subset with particular diagnostic and therapeutic approach.

Dealing with a heterogeneous disease as SSc, it is sometimes difficult cu distinguish the manifestations of the disease from an overlapping syndrome. In this regard, in the last years, many researchers have approached this field and discovered antibodies that can provide a better classification of SSc patients (9). In our study we bring evidence that dividing SSc patients not only in two groups (lcSSc and dcSSc) but also in a third one consisting of SSc patients with AIDs provides more information about their outcome, leading to a better tailored management. This is of major importance especially in a disease with such an unpredictable course as SSc. We have shown that SSc patients with AIDs tend to have a better outcome. Our study included a relatively small number of patients, which may account for not reaching statistical significance in the comparison regarding disease outcome. Even though, our data showed the same trend regarding the prognosis of SSc patients with AIDs as in an extended study on SSc-overlap patients, providing evidence that overlap patients have a better prognosis than patients with dcSSc but not as good as patients with lcSSc (10). Moreover, we included in our analysis also patients with other AIDs (not only overlap syndromes), but unfortunately we could not compare their outcome with lcSSc and dcSSc as separate subsets because of the small number of patients. Finally, other limitations of our study were loss to follow up of patients and missing data due to the limited access to immunological testing.

CONCLUSION

In conclusion, associated AIDs are rather frequent in SSc, affecting almost 20% of the patients. Taking in consideration the better outcome of patients with SSc and associated AIDs, they could be regarded as a separate subset of SSc.

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