SOCIEDADE BRASILEIRA DE REUMATOLOGIA

REVISTA BRASILEIRA DE REUMATOLOGIA

www.reumatologia.com.br

Original article

Overlap between systemic sclerosis and rheumatoid arthritis: a distinct clinical entity?

Alex Magno Coelho Horimoto[a,*], *Izaias Pereira da Costa*[a,b]

[a] *Universidade Federal de Mato Grosso do Sul, Campo Grande, MS, Brazil*
[b] *Universidade de São Paulo, São Paulo, SP, Brazil*

ARTICLE INFO

Article history:
Received 24 May 2014
Accepted 23 December 2014
Available online 13 July 2015

Keywords:
Systemic sclerosis
Rheumatoid arthritis
Overlap
Anticitrulin
Rheumatoid factor

ABSTRACT

Introduction: Systemic sclerosis (SSc) is an autoimmune disease of the connective tissue characterized by the triad of vascular injury, autoimmunity (cellular and humoral) and tissue fibrosis. It is estimated that musculoskeletal pain is a common complaint of patients with SSc, ranging from 40 to 80%, and mainly in patients with early diffuse disease. Arthritis, clinically observed, may be a feature seen in the presentation of SSc, often leading to early diagnostic errors with rheumatoid arthritis (RA). In the course of the disease, arthritis is observed in 24–97% of patients with SSc.

Objectives: To correlate the occurrence or nonoccurrence of arthritis in patients with SSc of the Midwest region of Brazil with possible distinct clinical and laboratory manifestations observed in three groups of patients. To report the frequency of true association between systemic sclerosis and rheumatoid arthritis in patients with clinically and radiologically observed synovitis.

Methods: Sixty-one SSc patients were subsequently assessed every 3 months within 1 year, in order to clinically observe the occurrence of synovitis and its patterns of progression. Patients were divided into 3 groups: 41 patients with SSc without arthritis, 16 SSc patients with arthritis and 4 patients with overlap of SSc and RA. All patients underwent a radiological examination of the hands at the end of the study.

Results: Among all patients evaluated, we found a female predominance (98.7%), mean age of 50.94 years, white color (49.2%), limited form of the disease (47.6%), time of diagnosis between 5 and 10 years (47.6%) and duration of the disease of 8.30 years. Among all patients, 14 (22.9%) had positive rheumatoid factor (RF), while among those with positive RF, only 10 patients had arthritis during one-year follow-up. The antibody anticitrulline (anti-CCP) test was performed in 24 patients, being positive in 4 of them (16.7%), with positivity being observed only in patients with SSc/RA overlap. Comparing the clinical manifestations among the groups of patients, there was a higher incidence of gastritis and cardiac valvulopathy in patients with SSc and arthritis, but not in the others. In the group of patients with SSc/RA overlap and in patients with SSc and arthritis a significant reduction in quality of life was observed, measured by HAQ index, especially in patients with arthritis present during clinical evaluation. We found radiographic changes in 42.6% of patients with SSc. However, in patients with synovitis, radiological changes consistent with rheumatoid arthritis were found in 50% of patients.

* *Corresponding author.*
E-mails: clinicaactivite@gmail.com, amchor@ibest.com.br (A.M.C. Horimoto).
http://dx.doi.org/10.1016/j.rbre.2014.12.011

Conclusions: While the frequency of clinical arthritis observed in patients with systemic sclerosis was 32.8%, the true overlap between of SSc and RA was 6.6% in this study. We also observed the frequency of positive anti-CCP in 20% of patients with arthritis versus no patients with SSc without arthritis.

Sobreposição de esclerose sistêmica e artrite reumatoide: uma entidade clínica distinta?

Palavras-chave:
Esclerose sistêmica
Artrite reumatoide
Sobreposição/overlap
Anticitrulina
Fator reumatoide

RESUMO

Introdução: A esclerose sistêmica (ES) é uma enfermidade do tecido conjuntivo de caráter autoimune caracterizada pela tríade de injúria vascular, autoimunidade (celular e humoral) e fibrose tecidual. Estima-se que a dor musculoesquelética seja uma queixa frequente dos pacientes com ES, oscilando entre 40 a 80% e principalmente em pacientes com doença difusa precoce. A artrite, clinicamente observada, pode ser uma característica observada na apresentação da ES, frequentemente levando a erros diagnósticos iniciais com artrite reumatoide (AR). No curso da enfermidade, a artrite é observada em 24 a 97% dos pacientes com ES.

Objetivos: Correlacionar a ocorrência ou não de artrite em pacientes com ES da região Centro Oeste do Brasil com possíveis manifestações clínicas e laboratoriais distintas observadas em três grupos de pacientes. Relatar a frequência de verdadeira associação entre esclerose sistêmica e artrite reumatoide em pacientes com sinovite clínica e radiologicamente observada.

Métodos: 61 pacientes portadores de ES foram avaliados subsequentemente a cada 3 meses durante o período de um ano, para fins de se constatar clinicamente a ocorrência de sinovite e padrões de evolução. Os pacientes foram divididos em 3 grupos: 41 pacientes com ES sem artrite, 16 pacientes com ES com artrite e 4 pacientes com sobreposição entre ES e AR. Todos os pacientes foram submetidos a exame radiológico das mãos no final do estudo.

Resultados: Dentre todos os pacientes avaliados, encontrou-se predomínio feminino (98,7%), idade média de 50,94 anos, cor branca (49,2%), forma limitada da doença (47,6%), tempo de diagnóstico entre 5 a 10 anos (47,6%)e tempo de evolução da doença de 8,30 anos. Entre todos os pacientes, 14 (22,9%) apresentavam fator reumatoide (FR) positivo, embora entre aqueles com FR positivo, apenas 10 pacientes apresentaram artrite durante o seguimento de um ano. O anticorpo anticitrulina (anti CCP) foi realizado em 24 pacientes, com positividade em 4 deles (16,7%), sendo a positividade observada somente nos pacientes com sobreposição ES/AR. Comparando-se as manifestações clínicas entre os grupos de pacientes, observou-se a maior ocorrência de gastrite e valvulopatia cardíaca em pacientes com ES e artrite, mas não nos demais grupos. No grupo de pacientes com *overlap* ES/AR e nos pacientes com ES e artrite observou-se redução importante de qualidade de vida, medido pelo índice HAQ, sobretudo nos pacientes com artrite presente no momento da avaliação clínica. Encontramos alterações radiográficas em 42,6% dos pacientes com ES. Contudo, nos pacientes com sinovite, encontrou-se alterações radiológicas compatíveis com artrite reumatoide em 50% dos pacientes.

Conclusões: Enquanto a frequência de artrite clínica observada em pacientes com esclerose sistêmica foi de 32,8%, a verdadeira sobreposição entre ES e AR foi de 6,6% neste estudo. Observou-se ainda a frequência de anti CCP positivo em 20% dos pacientes com artrite contra nenhum paciente com ES sem artrite.

Introduction

Systemic sclerosis (SSc) is an autoimmune disease of the connective tissue that is extremely heterogeneous in its clinical presentation, with involvement of multiple systems, following a variable and unpredictable course.[1] Its etiology remains unknown, with a multifactorial cause being suggested, possibly triggered by environmental factors in a genetically predisposed individual.[2]

SSc is mainly characterized by microvasculopathy, activation of fibroblasts and excessive collagen production.[3] This is a unique condition as it has characteristics of three distinct pathophysiological processes: it consists of the triad of vascular injury, autoimmunity (cellular and humoral) and

tissue fibrosis, leading to involvement of skin and several internal organs like lungs, heart, gastrointestinal tract, as well as musculoskeletal manifestations.[3,4]

It is estimated that musculoskeletal (ME) pain is a frequent complaint of SSc patients, ranging from 40 to 80% and especially in patients with early diffuse disease.[5] The main ME symptoms shown are movement limitations, joint pain and/or swelling.[6] Arthritis, clinically observed, may be a feature in the initial presentation of SSc, often leading to initial diagnostic errors with rheumatoid arthritis (RA).[7,8] In a series of cases described by Rodnan Medsger, Jr., in 41% of patients, arthritis or polyarthralgia was the first symptom, or developed within the first year after the onset of Raynaud's phenomenon.[8] In the course of the disease, arthritis is observed in 24–97% of patients with SSc.[6]

Joint lesions, ranging from periarticular osteopenia and joint space narrowing to apparent erosions, have been reported in the metacarpophalangeal, proximal interphalangeal and distal interphalangeal joints, as well as in the wrists.[5,6] According to Rodnan, the most common radiological abnormality seen in the bones and joints of patients with SSc was the resorption of the terminal phalanges (acroosteolysis), which was often followed by subcutaneous calcinosis.[8] In fact, after progression greater than 7 years of SSc, bone erosion was observed, especially in the hands, in 4–57% of patients, while joint space reduction was observed in 16–92% of cases.[5] Although many radiographic changes have been identified in the joints of patients with SSc, important erosive arthropathy is considered unusual.[9]

Synovial biopsies of the joints of patients with SSc showed evidence of varying severity of inflammation, and in most cases, an infiltrate of lymphocytes and plasma cells distributed diffusely in the tissue or collected in small focal aggregates was observed.[8] Unlike the findings observed in patients with RA, little or no tendency to the formation of pannus and intense synovial fibrosis later in the disease course was reported in SSc patients.[8]

There are isolated reports of erosive arthritis affecting wrists and hands, with radiological and serological features that are indistinguishable from those observed in RA.[10] However, it is still under discussion whether erosive arthritis is part of SSc, if it could be a manifestation of an overlap syndrome, or the manifestation of a different independent disease.[11] Whether rheumatoid arthritis and systemic sclerosis could coexist in the same patient has also been subject of much controversy.[6] While some studies associate erosive arthritis with the presence of rheumatoid factor, suggesting an association between the two diseases,[7,12] others have not confirmed these data.[10,11,13]

This study was expected to confirm the occurrence of typical clinical and laboratory manifestations in a subgroup of SSc patients with clinically and radiologically observed arthritis, as suggested by previous studies.

Objectives

To correlate the occurrence or nonoccurrence of arthritis in SSc patients from the Midwest region of Brazil with possible distinct clinical and laboratory manifestations observed in three groups of patients.

To report the true frequency of association between systemic sclerosis and rheumatoid arthritis in patients with clinically and radiologically observed synovitis.

Methods

This is an observational, analytical, and cross-sectional study.

The random selection of 61 patients was performed based on a survey of medical records from the Rheumatology Service of the University Hospital at the School of Medicine of the Federal University of Mato Grosso do Sul (FMUFMS).

For comparison, the patients were divided into 3 groups:

- 41 SSc patients without arthritis;
- 16 SSc patients with arthritis;
- 4 patients with overlap of SSc and RA.

The patients to be selected should meet the following criteria:

- Meet the new 2013 classification criteria for SSc[14];
- In the case of lack of skin thickening, they should meet the criteria of early SSc by LeRoy and Medsger 2001[15];
- For the diagnosis of true overlap with rheumatoid arthritis, the RA classification criteria of the 2010 ACR/EULAR were used,[16] and also the mandatory presence of anticitrulline antibody (anti-CCP) and/or typical radiological manifestations of the disease;
- Patients who had other associated infectious diseases or malignancies were excluded.

The information required for sociodemographic and clinical characterization of the disease was obtained from each patient's charts of medical records, and they were supplemented with patient interviews. In the first consultation, demographic and clinical data were collected, including disease duration, year of diagnosis, skin score of modified Rodnan,[17] presence of autoantibodies, thorough clinical examination and current treatment. Patients were subsequently assessed every 3 months during the first year, to clinically observe the occurrence of synovitis and its patterns of progression. All patients underwent a radiological examination of the hands at the end of the study.

Specific data on the Medsger's severity scale,[18] Valentini's activity criteria of the disease[19] and the *Scleroderma Health Assessment Questionnaire* (sHAQ)[20] were collected in the patient's initial assessment and also in a second evaluation, only in those who presented clinical evidence of synovitis.

Regarding serum samples, sera from patients previously selected and which were frozen at −50 °C and properly stored in the Laboratory of the University Hospital of UFMS were used for the research.

a. Antinuclear Antibodies (ANA)
   Indirect immunofluorescent technique was used for the analysis of ANA, having HEp2 cells as substrate (Faar

technique) and using the criteria of the II Brazilian consensus of antinuclear antibodies in Hep-2 cells (2003),[21] for the interpretation of the results.
Sera were considered positive if the title was greater than or equal to 160 and diluted until fluorescence became negative.

b. Anti-Sm, anti-RNP, anti-Jo1, anti-Ro (SSA) and anti-La (SSB) tests – enzyme immunoassay (ELISA) technique was used as previously described by McClain,[22] using substrate-specific kits for each test, following the manufacturer's specifications (Hemagen Diagnostics, Inc.). The test was considered positive when the value found was 3 times or more higher than *cut-off*.
c. Rheumatoid factor research – a technique of nephelometry was used and it was considered positive if the title was greater than 40 IU/ml.
d. Anti-CCP test – enzyme-linked immunosorbent assay (ELISA) technique was used, following the manufacturer's specifications (INOVA QUANTA LiteTM CCP3.1 IgG/IgA ELISA). The test was considered negative if <20 units, weakly reactive between 20 and 39 units, moderately reactive between 40 and 60 units, and highly reactive (high values) if >60 units.
e. For the anti-centromere research – indirect immunofluorescence technique was used, having HEp2 cells as substrate according to the criteria of the II Brazilian consensus of antinuclear antibodies in Hep-2 cells (2003),[21] for the interpretation of results.
f. For anti-DNA topoisomerase 1 (anti-Scl70) test – immunoassay technique was used,[23] using a specific kit QUANTA Lite TM Scl-70 from the laboratory INOVA (INOVA Diagnostics, Inc., San Diego, CA, USA) following the manufacturer's specifications. It was considered nonreactive if <20 units, weakly reactive between 20 and 39 units, moderately reactive between 40 and 80 units, and highly reactive (high values) if >80 units.
g. Anti-RNA polymerase III – ELISA technique was used as previously described,[24] using a specific kit QUANTA Lite RNA POL III ELISA from INOVA laboratory (INOVA Diagnostics, Inc., San Diego, CA, USA) following the manufacturer's specifications. It was considered negative if values <20 units, weakly reactive if between 20 and 39 units, moderately reactive between 40 and 80 units, and strongly reactive (higher values) if >80 units.

Statistical analysis

The comparison between patients with and without arthritis in relation to the quantitative variables evaluated in this study was performed using the Student *t*-test. The chi-square test was used to examine the association between presence and absence of arthritis with qualitative variables measured in this study. The results of the other variables evaluated in this study were presented in descriptive form or in the form of tables and graphs. Statistical analysis was performed using the software SPSS, version 20.0, considering a significance level of 5%.

Results

A total of 61 patients, with 60 (98.7%) being women and 1 (1.6%) a man, with a mean age of 50.94 ± 2.40 years (mean ± standard error of the mean), was found.

Of all patients, 30 (49.2%) patients were reported to be white, 28 (45.9%) patients were reported having brown color and 3 (4.9%) were reported being black.

Regarding the diagnosis, 58 (95.1%) patients diagnosed met the criteria for classification of 2013 ACR/EULAR for SSc. The 3 (4.9%) patients who did not meet these criteria, met the criteria by Leroy/Medsger for early SSc.

Regarding the clinical forms of the disease, 29 (47.6%) patients had the limited form, 20 (32.8%) patients had the diffuse form, 3 (4.9%) patients had the early form, 8 (13.1%) patients had the overlap form (1.6%) and 1 patient had the form sine scleroderma.

Regarding the time for diagnosis, 16 (26.2%) patients were diagnosed more than 10 years before, 29 (47.6%) patients were diagnosed between 5 and 10 years before, and 16 (26.2%) patients were diagnosed less than 5 years before. The progression of the disease in patients in general was 8.30 ± 1.01 years.

Among all patients, 14 (22.9%) were positive for rheumatoid factor. The positivity of rheumatoid factor was 9.8% in patients with SSc without arthritis, 37.5% in the SSc group with arthritis, and 100% in the group with SSc/RA overlap. The anticitrulline antibody (anti-CCP) was performed in 24 patients, being positive in 4 (16.7%) of these, with positivity being observed only in patients with SSc/RA association. Among patients with true SSc/RA overlap, half was of limited form ($n = 2$–50.0%), one patient was of diffuse form ($n = 1$–25.0%) and one patient had association with Sjögren syndrome ($n = 1$–25.0%).

The results regarding the epidemiological data and the monitoring index in SSc patients without arthritis, SSc with arthritis, and overlap SSc/RA are shown in Table 1. There was no significant difference between patients with SSc without arthritis, SSc with arthritis and SSc/RA overlap in relation to the quantitative variables age, time of Raynaud's phenomenon (RP) before diagnosis, disease duration not counting RP and monitoring indices (one-way ANOVA, p values ranging between 0.046 and 0.872; HQ2: Student's *t*-test, $p = 0.071$). Likewise, there was no association between the different experimental groups and the nominal or ordinal qualitative variables gender, color, time of diagnosis and clinical form (chi-square test, p value ranging from .758 to .941).

Table 2 shows the distribution of the patients evaluated in this study and results regarding skin, vascular and musculoskeletal disorders, in SSc patients without arthritis, SSc with arthritis, and overlap of SSc/RA. Overall, there was no association between the experimental groups and the variables related to skin, vascular and musculoskeletal manifestations observed in the patients evaluated in this study (chi-square test, p values ranging from 0.145 to 0.630). There was also no difference between patients with and without arthritis in relation to skin score (One-way ANOVA test, $p = 0.513$).

Except for gastritis ($p = 0.016$) and valvar heart disease ($p = 0.014$), in which SSc patients with arthritis (gastritis:

Table 1 – Demographic aspects and monitoring indexes in patients with SSc without arthritis, SSc with arthritis and SSc/RA overlap.

Variable	Group			*p* value
	SSc without arthritis	SSc with arthritis	SSc/RA overlap	
Epidemiological data				
Age	50.83 ± 1.96	50.31 ± 3.04	54.00 ± 8.18	0.872
Gender				
Male	1 (2.4)	0 (0.0)	0 (0.0)	0.780
Female	40 (97.6)	16 (100.0)	4 (100.0)	
Color				
White	20 (48.8)	9 (56.2)	1 (25.0)	0.758
Brown	19 (46.3)	6 (37.5)	3 (75.0)	
Black	2 (4.9)	1 (6.2)	0 (0.0)	
Time of diagnosis				
Less than 5 years	11 (26.8)	4 (26.7)	1 (25.0)	0.595
Between 5 and 10 years	17 (41.5)	8 (53.3)	3 (75.0)	
More than 10 years	13 (31.7)	3 (20.0)	0 (0.0)	
Time of RP before diagnosis	2.68 ± 0.84	5.56 ± 2.16	6.50 ± 4.57	0.235
Time of disease without counting RP	9.41 ± 1.05	7.44 ± 1.20	6.25 ± 1.03	0.396
Clinical form				
Limited	18 (43.9)	9 (52.6)	2 (50.0)	0.941
Diffuse	14 (34.1)	5 (31.2)	1 (25.0)	
Recent onset	3 (7.3)	0 (0.0)	0 (0.0)	
Overlap	5 (12.2)	2 (12.5)	1 (25.0)	
Sine	1 (2.4)	0 (0.0)	0 (0.0)	
Monitoring indexes				
sHAQ 1 (*n* = 61)	0.59 ± 0.07	0.71 ± 0.08	0.97 ± 0.17	0.163
sHAQ 2 (*n* = 20)	–	0.75 ± 0.08a	1.09 ± 0.14a	0.071[a]
Severity scale	5.29 ± 0.49	4.00 ± 0.53	4.50 ± 1.04	0.300
Activity scale	2.29 ± 0.21	2.50 ± 0.34	2.50 ± 0.68	0.854

SSc: systemic sclerosis, RA: rheumatoid arthritis, RP: Raynaud's phenomenon, sHAQ: Scleroderma Health Assessment Questionnaire.
The results are presented in median ± standard error of the median or absolute frequency (relative frequency). *p* value on one-way ANOVA test. Equal letters on line indicate that there is no significant difference among the groups after Tukey's test.

[a] *p* value on Student's *t*-test.

n = 7–43.8%, valvar disease: *n* = 7–100.0%) showed a higher percent of cases when compared with those with SSc without arthritis (gastritis: *n* = 5–12.2%; valvulopathy: *n* = 11–26.8%), there was no association between the experimental groups of SSc without arthritis, SSc with arthritis and SSc/RA overlap with variables related to other gastrointestinal, cardiopulmonary and renal manifestations observed in the patients evaluated in this study (chi-square test, *p* values ranging from 0.088 to 0.924). There was no significant difference between the experimental groups in relation to the quantitative variable pulmonary functional vital capacity (FVC) (One-way ANOVA test, $p = 0.313$). Moreover, it was not possible to compare patients with SSc without arthritis, SSc with arthritis, and SSc/RA overlap, regarding the estimated pulmonary artery pressure by echocardiography (EcoPSAP) as out of the 16 SSc patients with arthritis, this measure was only performed in one patient and was not performed in any patient with SSc/RA overlap. These results are shown in Table 3.

The results of the laboratory tests in SSc patients without arthritis, SSc with arthritis and SSc/RA overlap are shown in Table 4. There was no difference between patients with and without arthritis regarding erythrocyte sedimentation rate, C-reactive protein, creatine phosphokinase, C3 and C4 complements (one-way ANOVA, *p* value ranging from $p = 0.467$ to $p = 0.952$). Moreover, in relation to the results of the laboratory tests, there was no association between the experimental groups and the result for anti-Ro, anti-La, anti-Sm, anti-RNP, anti-Jo 1, anti-Scl 70, anticentromere and anti-RNA Pol 3, neither with the result regarding general changes in radiography (X-ray) of hands (chi-square test, value ranging from 0.073 to 0.816). On the other hand, the percentage of patients with overlapping SSc/RA who had a reduction in the joint space or subchondral erosions in the hands X-ray, or positive anti-CCP (*n* = 4–100.0%) was greater than that of patients with SSc with and without arthritis (*n* = 0–0.0%). Furthermore, the percentage of patients with SSc with arthritis and SSc/RA overlap who had positive rheumatoid factor (*n* = 6–37.5% *n* = 4–100.0%, respectively) was significantly higher than that of SSc patients without arthritis, who also showed positive rheumatoid factor (*n* = 4–9.8%; chi-square test, $p < 0.05$). These results are shown in Fig. 1.

Among the patients with arthritis (*n* = 20) the most frequently prescribed drugs were methotrexate (*n* = 9–45.0%), azathioprine (*n* = 7–35.0%), prednisone (*n* = 6–30.0%), chloroquine diphosphate (*n* = 6–30.0%), and leflunomide (*n* = 6–30.0%). These results are shown in Table 5.

Table 2 – Skin, vascular, and musculoskeletal manifestations, in patients with SSc without arthritis, SSc with arthritis and SSc/RA overlap.

Variable	Group			*p* value
	SSc without arthritis	SSc with arthritis	SSc/RA overlap	
Skin manifestations				
Calcinosis				
Yes	8 (19.5)	2 (12.5)	0 (0.0)	0.535
Hands				
With changes	32 (78.0)	15 (93.8)	3 (75.0)	
Findings on hands (n = 50)				
Edematous phase	10 (31.2)	7 (46.7)	0 (0.0)	0.197
Indurative phase	8 (25.0)	6 (40.0)	1 (33.3)	
Atrophic phase	14 (43.8)	2 (13.3)	2 (66.7)	
Skin Rodnan's score	13.66 ± 1.28	11.50 ± 1.76	16.00 ± 4.74	0.513
Vascular manifestations				
RP				
Objective	28 (68.3)	13 (81.2)	2 (50.0)	0.408
Subjective	13 (31.7)	3 (18.8)	2 (50.0)	
Microscars				
Yes	12 (29.3)	1 (6.2)	1 (25.0)	0.177
Active ulcers				
Yes	5 (12.2)	1 (6.2)	0 (0.0)	0.630
Necrosis or amputation				
Yes	6 (14.6)	0 (0.0)	0 (0.0)	0.197
Telangectasias				
Yes	26 (63.4)	11 (68.8)	4 (100.0)	0.327
Musculoskeletal manifestations				
Flexion contracture				
Yes	6 (14.6)	1 (6.2)	1 (25.0)	0.538
Tendon crepitation				
Yes	2 (4.9)	0 (0.0)	0 (0.0)	0.604
Muscle weakness				
Yes	7 (17.1)	1 (6.2)	0 (0.0)	0.401
Atrophy				
Yes	7 (17.1)	0 (0.0)	0 (0.0)	0.145

SSc: systemic sclerosis, RA: rheumatoid arthritis, RP: Raynaud's phenomenon.
The results are presented in median ± standard error of the median or absolute frequency (relative frequency). *p* value on one-way ANOVA test.

Discussion

Joint involvement with severe synovitis is relatively uncommon in patients with systemic sclerosis (SSc).[25] About 11% of SSc patients present with arthritis at the onset of the disease, usually characterized by mono- or oligoarthritis, responsive to corticosteroid therapy. However, some patients with SSc have more aggressive erosive arthritis, mimicking classic rheumatoid arthritis (RA).[25]

A rate of 6.6% of overlap with RA was observed in this study in 61 patients with SSc and musculoskeletal symptoms were very prevalent in these patients with or without association between the diseases, mainly represented by arthritis in almost a third of them. Other studies in Brazil found a higher prevalence of osteoarticular manifestations (47.7%),[26] with arthralgia ranging from 70.5% to 84.5%,[10,27,28] in addition to arthritis described in 17.6–44.4% of patients.[10,27] However, the prevalence of true overlap with RA has been described as being of 4.3–5.2% in other studies with patients with SSc.[6,11,12]

An important aspect observed in our patients was that the presence of arthritis contributed a lot to the functional deficit and lower quality of life measured by sHAQ. With sHAQ, much higher disability scores were observed in the second clinical evaluation in patients with arthritis, although a direct comparison with patients without arthritis was not possible. Morita and colleagues reported that patients with diffuse SSc had the highest rates of disability in HAQ, higher than those of patients with RA, SLE and other collagen vascular diseases.[29] It was also observed that patients with SSc and joint involvement had higher scores in HAQ than patients with psoriatic arthritis, while the pain domain was higher in SSc patients than in those with RA.[30] An association between HAQ and functional deficit caused by hands involvement has already been described.[31] In addition, it was described that the disability caused by the involvement of the hands in SSc patients who did not have RP at the time of evaluation was as severe as that observed in a population of patients with RA with comparable disease duration of 10 years.[20] The usefulness of HAQ in the evaluation of patients with SSc was demonstrated by studies that reported that it can predict the progress and survival in these patients.[32,33] In this work, there was a significant positive linear correlation between sHAQ in patients with arthritis and disease activity as measured by the Pearson test. Medsger and colleagues found that the HAQ disability indexes had strong

Table 3 – Gastrointestinal, cardiopulmonary and renal manifestations, in patients with SSc without arthritis, SSc with arthritis and SSc/RA overlap.

Variable	Group			*p* value
	SSc without arthritis	SSc with arthritis	SSc/RA overlap	
Gastrointestinal manifestations				
Involvement of esophagus				
Yes	30 (73.2)	9 (56.2)	3 (75.0)	0.447
Gastrointestinal symptoms				
GERD	9 (22.0)	5 (31.3)	2 (50.0)	0.414
Esophagitis	11 (26.8)	2 (12.5)	1 (25.0)	0.510
Gastritis	5 (12.2)b	7 (43.8)a	0 (0.0)ab	0.016
Esophageal hypotonia	6 (14.6)	1 (6.3)	2 (50.0)	0.088
Esophageal dilation	2 (4.9)	1 (6.3)	0 (0.0)	0.875
Cardiopulmonary manifestations				
FVC	81.83 ± 2.32	88.31 ± 3.47	85.00 ± 4.74	0.313
FVC – classification				
>80%	22 (53.7)	11 (68.8)	3 (75.0)	0.887
Between 70 and 80%	13 (31.7)	4 (25.0)	1 (25.0)	
Between 50 and 69%	4 (9.8)	1 (6.2)	0 (0.0)	
<50%	2 (4.9)	0 (0.0)	0 (0.0)	
Chest TC				
Altered	19 (46.3)	9 (56.2)	1 (25.0)	
Tomography findings (n = 29)				
Fibrosis	14 (73.7)	5 (55.6)	1 (100.0)	0.496
"Ground glass" pattern	5 (26.3)	4 (44.4)	0 (0.0)	
Echo PASP	31.23 ± 3.19 (*n* = 13)	42.00 (*n* = 1)	–	–
Result on echocardiogram				
Altered	26 (63.4)	7 (43.8)	1 (25.0)	
Findings on echocardiogram (n = 34)				
Valvulopathy	11 (26.8)b	7 (100.0)a	0 (0.0)ab	0.014
Concentric LVH	9 (22.0)	0 (0.0)	1 (100.0)	0.189
LV diastolic dysfunction	6 (14.6)	2 (28.6)	0 (0.0)	0.924
Mild or moderate PAH	5 (12.2)	1 (14.3)	0 (0.0)	0.668
Pericarditis	4 (9.8)	2 (28.6)	0 (0.0)	0.665
Renal manifestations				
Renal crisis				
Yes	1 (2.4)	0 (0.0)	0 (0.0)	0.780

SSc: systemic sclerosis, RA: rheumatoid arthritis, GERD: gastroesophagical reflux disease, FVC: pulmonary functional vital capacity, Echo PASP: estimated pressure on pulmonary artery on echocardiogram, LVH: left ventricular hypertrophy, PAH: pulmonary artery hypertension.
The results are presented in median ± standard error of the median or absolute frequency (relative frequency). *p* value on one-way ANOVA test. Equal letters on line indicate significant difference among the groups after Tukey's test.

correlation with skin thickening, cardiac involvement, digital contractures, tendon crepitation, and renal involvement in 1000 patients with SSc.[18]

The objective was to study, in this heterogeneous population of patients in the Midwest of Brazil, the correlation between the presence of clinical and radiological proven arthritis and the clinical and laboratory manifestations observed in patients with SSc. Patients with arthritis who were observed during the study period totaled 32.8% of all patients, with the majority presenting a pattern of mono- or oligoarthritis with remission after beginning the standard treatment for systemic sclerosis. However, of the 20 patients with demonstrated arthritis, 6 had a pattern of symmetrical and additive polyarthritis affecting large and small joints with prolonged morning stiffness, requiring the use of leflunomide with or without the use of methotrexate, among other medications. Of these 6 patients with persistent arthritis, 4 of them showed positive cyclic citrullinated antipeptid (anti-CCP), as well as joint space narrowing and/or subchondral erosions in the radiographs of hands, leading to the conclusion that there is clearly an overlap with rheumatoid arthritis, and it was necessary to combine rituximab to the therapeutic regimen of two patients to better control of composite indices of joint activity.

There are isolated reports of erosive arthritis affecting wrists and hands, with radiological and serological features that are indistinguishable from those observed in RA.[10] However, whether erosive arthritis is part of SSc, whether it could be a manifestation of an overlap syndrome or the manifestation of a different independent disease is still under discussion.[11] Whether rheumatoid arthritis and systemic sclerosis could coexist in the same patient has also been the subject of much controversy.[6] While some studies associate erosive arthritis with the presence of rheumatoid factor, suggesting an overlap between the two diseases,[7,12] others have not confirmed these data.[10,11,13] In our patients, although the presence of rheumatoid factor was related to the occurrence of arthritis in patients, only anti-CCP was undoubtedly related to the actual occurrence of overlap between SSc and RA, as well

Table 4 – Laboratory tests and radiographs of hands of patients with SSc without arthritis, SSc with arthritis and SSc/RA overlap.

Variable	Group			*p* value
	SSc without arthritis	SSc with arthritis	SSc/RA overlap	
ESR	28.49 ± 3.10	27.81 ± 6.44	25.00 ± 6.44	0.951
CRP	10.21 ± 2.67	14.34 ± 7.09	11.21 ± 6.28	0.792
CPK	130.24 ± 17.99	124.25 ± 18.13	68.25 ± 10.09	0.518
Creatinine	0.77 ± 0.04	0.70 ± 0.03	0.79 ± 0.03	0.467
C3	129.90 ± 4.52	127.50 ± 5.17	128.75 ± 2.87	0.952
C4	32.56 ± 1.76	31.19 ± 2.01	33.25 ± 1.89	0.884
Anti-Ro				
Positive	4 (9.8)	3 (18.8)	0 (0.0)	0.479
Anti-La				
Positive	0 (0.0)	1 (6.2)	0 (0.0)	0.239
Anti-Sm				
Positive	0 (0.0)	1 (6.2)	0 (0.0)	0.239
Anti-RNP				
Positive	7 (17.1)	2 (12.5)	1 (25.0)	0.816
Anti-Jo 1				
Positive	2 (4.9)	0 (0.0)	0 (0.0)	0.604
Hands X-ray				
Altered	18 (43.9)	6 (37.5)	4 (100.0)	
Findings on hands X-ray (n = 26)				
Calcinosis	6 (33.3)	3 (50.0)	0 (0.0)	0.249
Phalanges reabsorption	12 (66.7)	3 (50.0)	2 (50.0)	0.688
Space reduction/subchondral erosions	0 (0.0)b	0 (0.0)b	4 (100.0)a	<0.001
Anti-SCL 70				
Positive	10 (24.4)	5 (31.2)	2 (50.0)	0.519
Anti-centromere				
Positive	16 (39.0)	8 (50.0)	2 (50.0)	0.718
Anti-RNA Pol 3				
Positive	7 (17.1)	0 (0.0)	0 (0.0)	0.145
Rheumatoid factor				
Positive	4 (9.8)b	6 (37.5)a	4 (100.0)a	<0.001
Anti-CCP	(*n* = 4)	(*n* = 16)	(*n* = 4)	
Positive	0 (0.0)b	0 (0.0)b	4 (100.0)a	<0.001

SSc: systemic sclerosis, RA: rheumatoid arthritis, ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; CPK: creatine phosphokinase; C3: C3 complement fraction; C4: C4 complement fraction; X-ray: radiograph.
The results are presented in median ± standard error of the median or absolute frequency (relative frequency). *p* value on one-way ANOVA test. Equal letters on line indicate significant difference among the groups after Tukey's test.

as the finding of reduction of the joint space and subchondral erosions on radiographs of the hands of these patients.

The prevalence of an association between SSc/RA varies from 4.3 to 5.2% among patients with systemic sclerosis.[6,11,12] In addition, a higher incidence of RA in patients with SSc than in the general population was found.[34] It was suggested that this SSc/RA overlap is a distinct entity according to the different genetic background of patients: significantly increased frequencies of HLA-DR3 and HLA-DR11 were observed in SSc/RA compared with RA patients and healthy individuals; also, allele frequencies of HLA-DR1 and HLA-DR4 (shared epitopes) were significantly higher in SSc/RA and RA than in patients with SSc or controls.[12] However, the results obtained in a large cohort of European Caucasian patients with SSc did not support the involvement of genes (CCL21, CD244, CDK6) recently identified as of susceptibility to RA in these patients.[13]

Anyway, the genetic link is the best explanation for the occurrence of SSc/RA overlap.[35] Several studies have shown that autoimmune diseases are grouped in families of patients with SSc.[36–39] In a population with 719 patients with SSc, RA was the second most prevalent disease in a study of polyautoimmunity (21%) and the most commonly observed in familial autoimmunity (18%).[34] This supports the concept that these diseases can arise in a shared genetic basis underlying various autoimmune phenotypes, with overlap between SSc/RA being only one of these phenotypes.

Szücs et al. described, in patients with overlap between SSc/RA, a combination of characteristic clinical manifestations, both for SSc and RA, with erosive polyarthritis in 82%, pulmonary fibrosis in 77%, esophageal involvement in 55%, and cardiovascular manifestations, while kidney involvement occurred in 23% of patients.[12] A single clinical and

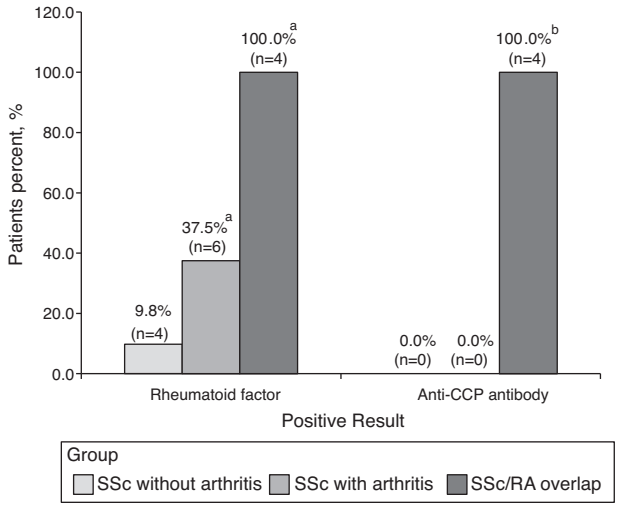

Fig. 1 – Graph showing the percentage of patients with rheumatoid factor or positive or negative anti-CCP antibody, among SSc patients without arthritis, SSc with arthritis, and overlapping SSc/RA. Each column represents the percentage of patients. [a] Significant difference in relation to SSc patients without arthritis (chi-square test, $p < 0.001$). [b] Significant difference in relation to SSc patients without arthritis and SSc with arthritis (chi-square test, $p < 0.001$). SSc: systemic sclerosis, RA: rheumatoid arthritis.

serological pattern was also reported, since most patients with overlap were those of limited form, with positivity of anti-topoisomerase in 23% of patients but positive anti-centromere in only 9%.[12] However, in this study we found in patients with SSc/RA overlap an equal proportion of patients with limited and diffuse forms, and 50% of positivity of the topoisomerase and the anticentromere. Moreover, when comparing the clinical manifestations of patients of the group with arthritis, even the SSc/RA overlap subgroup, to the group of SSc patients without arthritis, we could not confirm that the SSc/RA overlap is an entity clinically distinct from mere association of SSc and RA.

The presence of rheumatoid factor (RF) has been observed in up to 25% of patients with SSc,[6] in agreement with the present study, which found a positivity rate of RF of 22.9% among 61 patients. In our case, the presence of arthritis correlated significantly with FR positivity. Misra et al. found RF positivity in 80% of patients with degenerative arthritis compared with 13% positivity in other patients with SSc.[6] We found positive FR in 50% of patients with arthritis and in 100% of patients with degenerative arthritis related to radiographic changes, against 9.8% of patients with SSc without arthritis. In the latter group of patients, rheumatoid factor was probably related to the overlap syndrome, since the 4 patients in this group with positive RF had an association with Sjögren's syndrome.

Recently, through the availability of the cyclic citrullinated antipeptide tests (anti-CCP), the percentage of association with positive anti-CCP RA has been reported in 1–15% of patients with SSc.[5] A statistically significant correlation between the anti-CCP positivity and the presence of arthritis with marginal erosions in patients with SSc is described, which could aid in the diagnosis of overlap of SSc and RA, and enable appropriate treatment.[9] However, anti-CCP antibodies by themselves do not define rheumatoid arthritis, since the frequency of positivity of these antibodies in patients with SSc without arthritis is not known.[5] We found anti-CCP positivity in 20% of SSc patients with arthritis and present in 100% of patients with degenerative arthritis related to radiographic changes, versus no SSc patients without arthritis.

Radiographic changes were found in 42.6% of the SSc patients, particularly characterized by resorption of the distal phalanges (65.4%) and calcinosis (34.6%) in both groups with and without arthritis. However, in patients with synovitis presenting changes on radiographs of the hands, radiological changes compatible with rheumatoid arthritis were observed in 50% of these patients, characterized by joint space narrowing and/or subchondral erosions. These RA-like changes were only found in 4 patients with diagnosis of SSc/RA overlap. However, both in patients with SSc and arthritis or patients with SSc/RA overlap, the presence of resorption of the distal phalanges and calcinosis was seen, but these pathognomonic changes of SSc were observed less commonly in the second group. Meanwhile, Allali et al. found radiographic changes in 80% of 46 patients with SSc who had arthritis, including joint space narrowing in 37% and erosions in 43% of these patients.[9] The same researcher found that the most common sites of occurrence of erosions were the proximal interphalangeal and radiocarpal joints.[9] In a cohort of 58 patients with SSc, Schmeiser et al. found signs of arthritis in 31% of patients, with 19% being clinical and 26% radiological. In a meta-analysis of seven studies, we found a prevalence of 26% of radiologically detectable arthritis in patients with SSc.[11]

The higher incidence of gastritis and cardiac valvulopathy observed only in patients with SSc and arthritis, but not in the other groups, can be explained by the more sustained use, and in greater amounts, of non-steroid anti-inflammatory drugs (NSAIDs) for joint pain. The group of patients with SSc/RA overlap, despite a persistent arthritis, promptly began taking disease-modifying anti-rheumatic drugs (DMARDs) rather than using NSAIDs. The blockade of cyclooxygenase caused by the use of NSAIDs reduces the production of inflammatory prostaglandins, altering the balance of vasoconstrictor and dilator factors, contributing to water retention and high

Table 5 – Most frequently used drugs in patients with arthritis.

Drugs (among patients with arthritis – $n = 20$)	(n) %
Non-steroidal anti-inflammatories	13 (65.0)
Methotrexate	9 (45.0)
Azathioprine	7 (35.0)
Prednisone	6 (30.0)
Chloroquine diphosphate	6 (30.0)
Leflunomide	6 (30.0)
Rituximab	2 (10.0)

The results are presented in absolute frequency (relative frequency).

blood pressure, leading to decompensation of heart failure and valvulopathies.[40,41] Study patients with SSc and arthritis had a higher association with systemic hypertension (unpublished data) and the two study patients with SSc and arthritis, who had valvulopathies, showed no association with rheumatic fever, systemic lupus erythematosus or antiphospholipid syndrome.

Regarding the use of DMARDs, the literature is scarce about the use of leflunomide (LFD) in systemic sclerosis. Sebastiani et al. observed that LFD was able to improve arthritis related to SSc in 3 patients. Moreover, organ involvement remained stable in 2 cases, while skin sclerosis improved in the other patient.[25]

The efficacy of rituximab (RTX) as a modifying drug in patients with rheumatoid arthritis is well documented. In patients with SSc its use appears to be safe and well tolerated.[42–44] A controlled study prior to RTX indicated that it can improve lung function in patients with SSc,[42] and a skin improvement was described with the use of modified Rodnan score[42–44] or histological methods,[42,44] which could suggest a potential role of disease-modification in the pathophysiological process of fibrosis in SSc by B lymphocyte depletion. In RA, the effective clinical response was not necessarily correlated with the degree of B-cell infiltration in synovial tissues before treatment.[43] But since the local infiltration of B cells is an important component of the mode of action of RTX, Lafyatis et al. highlight that this therapy may be more effective when the target tissues show infiltrates full of B cells, such as pulmonary fibrosis associated with SSc.[43]

Biological blockers of tumor necrosis factor (anti-TNF) were not used in our patients, although they proved to be useful and effective in the treatment of arthritis associated with inflammatory SSc.[45–48] Bosello et al. suggested that the use of anti-TNF in medium-term could also be beneficial to reduce the progression of fibrotic disease and control of ulcerations,[46] but other studies did not observe any improvement in the skin score and in the pulmonary function with therapy.[45,47] Moreover, Omair et al. reported malignancies (breast cancer, basal cell carcinoma and leukemia) in a third of patients receiving anti-TNF therapy[47] and now the European group of experts on the scleroderma and systemic sclerosis trials and research (EUSTAR) does not recommend the routine use.[48]

Regarding the use of other biologicals in SSc, they were not necessary in our patients with arthritis due to a good response with the use of rituximab, although the EUSTAR group concluded in an observational study that tocilizumab and abatacept appeared to be safe and effective in the treatment of refractory polyarthritis in patients with SSc, but there were no significant changes in lung or skin fibrosis in both groups.[49]

The weakness of the study was the heterogeneity of the study population, patients with long clinical staging of the disease, and also the small number of patients in the SSc/RA overlap group. The relevance of this study is that it described, for the first time in the country, the clinical laboratory features of this overlap in patients with SSc. Moreover, this study confirms the important role of radiographs of the hands, of rheumatoid factor, and anti-CCP in the evaluation of arthritis in patients with SSc, and it is possible to correlate the positivity of both antibodies with the occurrence of association between SSc and RA.

Conclusions

While the frequency of clinical arthritis observed in patients with scleroderma was 32.8%, the true overlap between systemic sclerosis and rheumatoid arthritis was 6.6% in this study.

Except for a higher incidence of gastritis and heart valve disease, there were no distinct clinical manifestations in patients with SSc and presence of arthritis compared with a group of patients without arthritis.

However, the percentage of patients with arthritis who had radiographic changes, and positive rheumatoid factor, was significantly higher than those of the SSc patients without arthritis. We also observed the frequency of positive anti-CCP in 20% of patients with arthritis versus no patients with SSc without arthritis.

Conflicts of interest

The authors declare no conflicts of interest.

REFERENCES

1. Varga J, Abraham D. Systemic sclerosis: a prototypic multisystem fibrotic disorder. J Clin Invest. 2007;117(3):557–67.
2. Herrick AL, Worthington J. Genetic epidemiology: systemic sclerosis. Arthritis Res. 2002;4(3):165–8.
3. Coral-Alvarado P, Pardo AL, Castaño-Rodriguez N, Rojas-Villarraga A, Anaya JM. Systemic sclerosis: a world wide global analysis. Clin Rheumatol. 2009;28:757–65.
4. Beyer C, Schett G, Gay S, Distler O, Distler JHW. Hypoxia in the pathogenesis of systemic sclerosis. Arthritis Res Ther. 2009;11:220–9.
5. Clements PJ, Allanore Y, Khanna D, Singh M, Furst DE. Arthritis in systemic sclerosis: systematic review of the literature and suggestions for the performance of future clinical trials in systemic sclerosis arthritis. Semin Arthritis Rheum. 2012;41:801–14.
6. Misra R, Darton K, Jewkes RF, Black CM, Maini RN. Arthritis in scleroderma. Br J Rheumatol. 1995;34:831–7.
7. Catoggio LJ, Evison G, Harkness JAL, Maddison PJ. The arthropathy of systemic sclerosis (scleroderma); comparison with mixed connective tissue disease. Clin Exp Rheumatol. 1983;1:101–12.
8. Rodnan GP, Medsger TA Jr. The rheumatic manifestations of progressive systemic sclerosis (scleroderma). Clin Orthop Rel Res. 1968;57:81–92.
9. Allali F, Tahiri L, Senjari A, Abouqal R, Hajjaj-Hassouni N. Erosive arthropathy in systemic sclerosis. BMC Public Health. 2007;7:260.
10. Fernandes SEM, Marques Neto JF, Finetti RMI, Samara AM. Manifestações osteoarticulares na esclerose sistêmica. Rev Bras Reumatol. 1988;28(3):65–9.
11. Schmeiser T, Pons-Kühnemann J, Özden F, Müller-Ladner U, Dinser R. Arthritis in patients with systemic sclerosis. Eur J Intern Med. 2012;23:25–9.
12. Szücs G, Szekanecz Z, Zilahi E, Kapitány A, Baráth S, Szamosi S, et al. Systemic sclerosis-rheumatoid arthritis overlap syndrome: a unique combination of features suggests a

distinct genetic, serological and clinical entity. Rheumatology. 2007;46:989–93.
13. Coustet B, Dieude P, Wipff J, Avouac J, Hachulla E, Diot E, et al. Association study of 3 rheumatoid arthritis risk loci in systemic sclerosis in a European caucasian population. Clin Exp Rheumatol. 2011;29(65):S6–9.
14. Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. Ann Rheum Dis. 2013;72:1747–55.
15. LeRoy EC, Medsger TA Jr. Criteria for the classification of early systemic sclerosis. J Rheumatol. 2001;28(7):1573–6.
16. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO III, et al. 2010 Rheumatoid arthritis classification criteria. An American College of Rheumatology/European League Against Rheumatism collaborative initiative. Arthritis Rheum. 2010;62(9):2569–81.
17. Valentini G, D'Angelo S, Rossa AD, Bencivelli W, Bombardieri S. European Scleroderma Study Group to define disease activity criteria for systemic sclerosis. IV. Assessment of skin thickening by modified Rodnan skin score. Ann Rheum Dis. 2003;62:904–5.
18. Medsger TA Jr. Natural history of systemic sclerosis and the assessment of disease activity, severity, functional status, and psychologic well-being. Rheum Dis Clin North Am. 2003;29:255–73.
19. Valentini G, Silman AJ, Veale D. Assessment of disease activity. Clin Exp Rheumatol. 2003;21(S29):S39–41.
20. Rannou F, Poiraudeau S, Berezné A, Baubet T, Le-Guern V, Cabane J, et al. Assessing disability and quality of life in systemic sclerosis: construct validities of the Cochin hand function scale, health assessment questionnaire (HAQ), systemic sclerosis HAQ, and medical outcomes study 36-item short form health survey. Arthritis Rheum. 2007;57(1):94–102.
21. Dellavance A, Gabriel A Jr, Cintra AFU, Ximenes AC, Nuccitelli B, Tabilerti BH, et al. II Consenso Brasileiro de Fator Antinuclear em células Hep-2. Rev Bras Reumatol. 2003;43(3):129–40.
22. McClain MT, Ramsland PA, Kaufman KM, James JA. Anti-Sm autoantibodies in systemic lupus target highly basic surface structures of complexed spliceosomal autoantigens. J Immunol. 2002;168:2054–62.
23. Sato S, Hamaguchi Y, Hasegawa M, Takehara K. Clinical significance of anti-topoisomerase I antibody levels determined by Elisa in systemic sclerosis. Rheumatology. 2001;40:1135–40.
24. Codullo V, Morozzi G, Bardoni A, Salvini R, Deleonardi G, Pità O, et al. Validation of a new immunoenzymatic method to detect antibodies to RNA polymerase III in systemic sclerosis. Clin Exp Rheumatol. 2007;25:373–7.
25. Sebastiani M, Giuggioli D, Vesprini E, Caruso A, Ferri C. Successful treatment with leflunomide of arthritis in systemic sclerosis patients. Rheumatology. 2006;45:1175–6.
26. Sampaio-Barros PD, Bortoluzzo AB, Marangoni RG, Rocha LF, Del Rio APT, Samara AM, et al. Survival, causes of death, and prognostic factors in systemic sclerosis: analysis of 947 Brazilian patients. J Rheumatol. 2012;39:1971–8.
27. Skare TL, Luciano AC, Fonseca AE, Azevedo PM. Autoanticorpos em esclerodermia e sua associação ao perfil clínico da doença. Estudo em 66 pacientes do sul do Brasil. An Bras Dermatol. 2011;86(6):1075–81.
28. Jezler SFO, Santiago MB, Andrade TL, Araujo Neto C, Braga H, Cruz AA. Comprometimento do interstício pulmonar em portadores de esclerose sistêmica progressiva. Estudo de uma série de 58 casos. J Bras Pneumol. 2005;31(4):300–6.
29. Morita Y, Muro Y, Sugiura K, Tomita Y, Tamakoshi K. Results of the Health Assessment Questionnaire for Japanese patients with systemic sclerosis – measuring functional impairment in systemic sclerosis versus other connective tissue diseases. Clin Exp Rheumatol. 2007;25:367–72.
30. Pope J. Measures of systemic sclerosis (Scleroderma). Arthritis Care Res. 2011;63(S11):S98–111.
31. Merkel PA, Herlyn K, Martin RW, Anderson JJ, Mayes MD, Bell P, et al. Measuring disease activity and functional status in patients with scleroderma and Raynaud's phenomenon. Arthritis Rheum. 2002;46(9):2410–20.
32. Georges C, Chassany O, Mouthon L, Tiev K, Toledano C, Meyer O, et al. Validation of French version of the Scleroderma Health Assessment Questionnaire (SSc HAQ). Clin Rheumatol. 2005;24:3–10.
33. Danieli E, Airò P, Bettoni L, Cinquini M, Antonioli CM, Cavazzana I, et al. Health-related quality of life measured by the Short Form 36 (SF-36) in systemic sclerosis: correlations with indexes of disease activity and severity, disability, and depressive symptoms. Clin Rheumatol. 2005;24:48–54.
34. Hudson M, Rojas-Villarraga A, Coral-Alvarado P, López-Guzmán S, Mantilla RD, Chalem P, et al. Polyautoimmunity and familial autoimmunity in systemic sclerosis. J Autoimmun. 2008;31:156–9.
35. Agarwal SK, Tan FK, Arnett FC. Genetics and genomic studies in scleroderma (systemic sclerosis). Rheum Dis Clin North Am. 2008;34(1):17–40.
36. Koumakis E, Dieudé P, Avouac J, Kahan A, Allanore Y. Familial autoimmunity in systemic sclerosis – results of a French-based case–control family study. J Rheumatol. 2012;39:532–8.
37. Hemminki K, Li X, Sundquist J, Sundquist K. Familial associations of rheumatoid arthritis with autoimmune diseases and related conditions. Arthritis Rheum. 2009;60(3):661–8.
38. Jawaheer D, Seldin MF, Amos CI, Chen WV, Shigeta R, Monteiro J, et al. A genomewide screen in multiplex rheumatoid arthritis families suggests genetic overlap with other autoimune diseases. Am J Hum Genet. 2001;68:927–36.
39. Caramaschi P, Biasi D, Volpe A, Carletto A, Cecchetto M, Bambara LM. Coexistence of systemic sclerosis with other autoimmune diseases. Rheumatol Int. 2007;27:407–10.
40. McGettigan P, Henry D. Current problems with non-specific COX inhibitors. Curr Pharm Des. 2000;6(17):1693–724.
41. Brooks PM, Kean WF, Kassam Y, Buchanan WW. Problems of antiarthritic therapy in the elderly. J Am Geriatr Soc. 1984;32(3):229–34.
42. Daoussis D, Liossis SNC, Tsamandas AC, Kalogeropoulou C, Kazantzi A, Sirinian C, et al. Experience with rituximab in scleroderma: results from a 1-year, proof-of-principle study. Rheumatology. 2010;49:271–80.
43. Lafyatis R, Kissin E, York M, Farina G, Viger K, Fritzler MJ, et al. B cell depletion with rituximab in patients with diffuse cutaneous systemic sclerosis. Arthritis Rheum. 2009;60(2):578–83.
44. Smith V, Praet JTV, Vandooren B, Der Cruyssen BV, Naeyaert JM, Decuman S, et al. Rituximab in diffuse cutaneous systemic sclerosis: an open-label clinical and histopathological study. Ann Rheum Dis. 2010;69:193–7.
45. Phumethum V, Jamal S, Johnson SR. Biologic therapy for systemic sclerosis: a systematic review. J Rheumatol. 2011;38:289–96.
46. Bosello S, De Santis M, Tolusso B, Zoli A, Ferraccioli G. Tumor necrosis fator-α inhibitor therapy in erosive polyarthritis secondary to systemic sclerosis. Ann Intern Med. 2005;143(12):918–20.
47. Omair MA, Phumethum V, Johnson SR. Long-term safety and effectiveness of tumour necrosis factor inhibitors in systemic sclerosis patients with inflammatory arthritis. Clin Exp Rheumatol. 2012;30(71):S55–9.

48. Distler JHW, Jordan S, Airò P, Alegre-Sancho JJ, Allanore Y, Gurman AB, et al. Is there a role for TNF-α antagonists in the treatment of SSc? EUSTAR expert consensus development using the Delphi technique. Clin Exp Rheumatol. 2011;29(65):S40–5.

49. Elhai M, Meunier M, Matucci-Cerinic M, Maurer B, Riemekasten G, Leturcq T, et al. Outcomes of patients with systemic sclerosis-associated polyarthritis and myopathy treated with tocilizumab or abatacept: a Eusar observational study. Ann Rheum Dis. 2013;72:1217–20.