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Sjögren's Syndrome and Sicca Symptoms in Patients with Systemic Sclerosis

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Abstract

Introduction: Several autoimmune diseases can be accompanied by dysfunction of the salivary glands, regardless of the presence or absence of association with Sjögren's syndrome (SS). A recent study by Maeshima et al. found salivary hyposecretion in 58.3% of patients with various connective tissue diseases, particularly systemic sclerosis (SSc).

Objective: To determine the prevalence of SS and sicca symptoms in patients with SSc. Assess whether the presence of SS in patients with SSc causes worsening of the disease.

Methods: 69 SSc patients periodically monitored in the rheumatology clinic at NHU / UFMS composed the study. All patients were questioned about sicca symptoms and clinical features. We evaluated the RF levels, ANA, anti-Ro / La.

Results and discussion: 69 SSc patients were enrolled in the study, with average age of 51.2 years, women at 98.3% and white by 50%. Sicca symptoms were present in 48 patients (69.5%) with SSc; 43/69 patients (62.3%) with dry mouth and 46/69 patients (66,7%) with dry eye. Sicca symptoms observed predominantly in patients with diffuse disease (75%). The antinuclear antibody positivity was 95% and the rheumatoid factor (RF) was observed in 14 patients (23.3%). Anti-Ro (SSA) were detected in 11 patients (15.9%) antibodies and anti-La (SSB) in 6 patients (8.7%) in this study. Only 16 patients (23.2%) had true SS, according to the American-European Consensus Group on Classification Criteria for Sjögren's syndrome. The findings in the study corroborate data found in literature. Koback et al. found similar data, 68% of patients with the limited form presented sicca symptoms, RF was present in 19.2% and anti-Ro in 10.3%. Hyposecretion salivary study in patients without SS found significant differences between groups, being much higher in the SSc group compared to patients with SLE, RA, MCTD and myopathies.

Conclusion: This study confirms that sicca symptoms are found in large numbers of patients with SSc. SS prevalence was observed in 23.2% of the SSc patients, mainly in patients of diffuse form of the disease. We conclude that the presence of SS did not change positively or negatively the severity or the clinical manifestations observed in patients with SSc.

Keywords: Sicca syndrome; Sjögren's syndrome; Overlap; Autoantibodies; Systemic sclerosis

Introduction

Systemic sclerosis (SSc) is a complex polygenic disease that manifests in genetically predisposed individuals with exposure to environmental factors or precipitating [1]. Its pathogenesis is characterized by three major features: vasculopathy of the small vessels, autoantibody production and fibroblast dysfunction leading to an increased deposition in the extracellular matrix [2]. Clinical manifestations and SSc prognosis varies, with most of patients presenting thickening of the skin and a wide internal organ involvement [1,2]. Sjögren's syndrome (SS) can be primary or be present in a context of other connective tissue disease, most commonly rheumatoid arthritis and systemic lupus erythematosus, but may be present in patients with SSc [3,4]. The first report of an association between SSc and SS was made in 1965 by Bloch et al. [3] who reported this association in 3 patients. Subsequently, several studies have reported the existence of a distinct clinical phenotype in patients with SSc in association with SS, particularly in patients with limited form with positivity for anti-centromere [4-8]. To enhance the complexity of this association, it has increased the number of patient's subgroup reports with SS with positivity for anti-centromere, but no association or evolution for SSc, considered a distinct clinical variant of primary Sjögren [8]. Although sicca symptoms are common in SSc patients (60 to 71.2%), due to a fibrosis of salivary gland [3,4,9,10], the true SS is present in only 10.3 to 33.9% of these patients [3,4,10,11]. Few data exist describing the association between SSc and SS, and the data do not show compliance to characterize the SS in SSc patients [4,9]. Typically, secondary Sjögren's syndrome is different from Sjögren syndrome associated [9]. The SS secondary to rheumatoid arthritis appears to to be more a complication, presenting a less aggressive sicca syndrome, anti-Ro / SSA and anti-La / SSB less frequently and the evolution of SS following the evolution of rheumatoid arthritis [3,9]. On the other hand, SS accompanying systemic lupus erythematosus (SLE), or autoimmune thyroiditis shows a serological and clinical

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pattern similar to the primary SS with the same instance of anti-Ro / SSA and anti-La / SSB and the same severity as the primary SS [3,9]. In this way the SS seems to be associated with these disorders as an overlap syndrome [4]. Moreover, the association of SS with other autoimmune disease can modify the severity of autoimmune disease associated [9]. It is speculated that SS associated with SSc could worsen the evolution and prognosis of these patients, however there are few studies describing the association [3,9].

Objectives

To determine the prevalence of SS and sicca symptoms in patients with SSc. To evaluate if the presence of SS in patients with SSc causes aggravation of the disease, determining if the severity or the clinical manifestations of these diseases change when they are associated.

Methods

This is an observational and comparative study of 69 patients treated at the Rheumatology Clinic of UFMS University Hospital, diagnosed with SSc and SS and compares them with patients diagnosed with SSc but without SS. The selection of 69 patients at random, was made from the survey of Medical Records from the University Hospital Rheumatology Department of the Faculty of Medicine of the Federal University of Mato Grosso do Sul (FMUFMS) during the period from February 2014 to March 2015.

The patients were divided into 2 groups:

- The first consisting of 16 patients with overlap between SS and SSc;
- The second consisting of 53 SSc patients without SS, but they could have or not sicca symptoms.

Patients to be selected should meet the following criteria:

For systemic sclerosis

- Fulfill the new classification criteria ACR / EULAR 2013 from 2013 for systemic sclerosis [12].
- In the case of absence of skin thickening, they should fill the early SSc criteria of LeRoy and Medsger 2001 [13].
- The study was approved by the local Ethics Committee (Plataforma Brasil number: 818.636, CAAE: 31475914.0.0000.0021), and all of the participants provided written informed consent.

For sjögren's syndrome

The diagnosis was based on the American-European Consensus Group on Classification Criteria for Sjögren's syndrome [14].

Exclusion

- Patients who had other associated infectious diseases or malignant neoplasms were excluded;
- Indigenous patients, pregnant women and children were excluded.

The information needed to characterize sociodemographic and clinical of the disease were obtained from medical registers in the medical records of each patient and supplemented by patient interviews. At the first visit were collected demographic and clinical data, including disease duration, year of diagnosis, skin score of modified Rodnan [15], autoantibody research, full clinical examination and current treatment. All patients were asked about symptoms of ocular and oral dryness by adapting the standard questionnaire for sicca symptoms [14] (Table 1).

Quantitative variables were analyzed

Age, Raynaud's phenomenon of time (RP) before diagnosis, disease duration not counting the RP and monitoring indices, as well as nominal or ordinal qualitative variables such as sex, color, time of diagnosis and diagnostic criteria. Other manifestations evaluated in these SSc patients associated or not to SS referred to the cutaneous, vascular, musculoskeletal, cardiopulmonary and kidney manifestations. Laboratory tests were also analyzed in these patients, the main ones being: ESR, CRP, CPK, Creatinine, C3 and C4 and immunological tests such as ANA, anti-centromere, anti-DNA topoisomerase I, anti-RNA polymerase 3, rheumatoid factor, anti-Ro (SSA), anti-La (SSB), anti-RNP, anti-Sm and anti-Jo. Specific data on the Medsger Severity criteria [16], Valentini Activity criteria of the disease [17] and Scleroderma Health Assessment Questionnaire (sHAQ) [18] were collected in the initial evaluation of the patient. With respect to serum samples that were used for the research, sera from the previously selected patients that were properly frozen to -50° C and stored in the Laboratory of the University Hospital of UFMS.

Antinuclear antibodies (ANA): The indirect immunofluorescence technique was used for the analysis of ANA and having as substrate the HEp2 cells (Faar technique) and used the criteria of the II Brazilian Consensus on Antinuclear factor in Hep-2 cells (2003) [19] for the interpretation of the results. Sera were considered positive if title was greater than or equal to 160 and diluted until obtain the negativity of the fluorescence.

Anti-Sm, anti-RNP, anti-Jo1, anti-Ro (SSA) and anti-La (SSB) researches: This was used immunoenzymatic assay technique (ELISA) as previously described by McClain [20], using specific substrate kits for each test, following the manufacturer's specifications. (Hemagen Diagnostics, Inc). It was considered positive serum that has 3 times the cut-off. Rheumatoid Factor Research - Nephelometry technique was used and considered positive if the title was greater than 40 Ui / ml [21]. For anticentromere (ACA) research - the indirect immunofluorescence technique was used and had as substrate the HEp2 cells according to the criteria of the II Brazilian Consensus on Antinuclear factor in Hep-2 cells (2003) [19] for the interpretation of the results. For the anti-DNA topoisomerase 1 (anti-Scl70) research - was used immunoenzymatic assay technique [22] using a specific kit QUANTA Lite TM Scl-70 from INOVA Laboratory (INOVA Diagnostics, Inc., San Diego, CA, USA), following the manufacturer's specifications. It was considered not reactants if < 20 units, weakly reactants between 20 and 39 units, moderately reactants between 40 and 80 units and highly reactants (high values) if > 80 units. Anti-RNA polymerase III antibody (anti POL3) - was used ELISA technique as previously described [23],

Eye symptoms
Is there daily and persistent eye problems related to dry eye chart for more than three months?
Is there any feeling of sand or ocular burning?
Is there usage of lubricating eye drops more than three times a day?
Oral symptoms
Is there any feeling of dry mouth for more than three months?
Is there recurrent or persistent swelling of the salivary glands as an adult?
Do you need to drink liquids to aid in swallowing solid food?
Adaptation of the American-European Consensus Group on Classification Criteria for Sjögren's syndrome (Vitali et al. [14]).

Table 1: Standardized questionnaire to sicca syndrome.

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. They were considered negative values < 20 units, weakly reactants between 20 and 39 units, moderately reactants between 40 and 80 units and strongly reagents (higher values) if > 80 units.

Statistical analysis

The comparison between patients with SSc associated with SS, with those without this association, in relation to the quantitative variables evaluated in this study, was performed using the t-student test. The chi-square test was used to assess the association between the results for SS (present or absent), with qualitative variables measured in this study. The results of the other variables assessed in this study were presented in the form of descriptive statistics or in tables and graphs. Statistical analysis was performed using the "software" SPSS, version 20.0, assuming a significance level of 5% [24].

Results

The results related to epidemiological data and monitoring index in SSc patients with SS present or absent, are shown in Table 2. There was no significant difference between patients with SSc and SS present or absent in relation to the quantitative variables age, RP time prior to diagnosis, disease duration after diagnosis and monitoring indexes (t-student test, p values ranging from 0.411 and 0.938). There was also no association between the presence of SS and the nominal or ordianl qualitative variables sex, race, clinical form and time of diagnosis (chi-square test, p value ranging between 0.197 and 0.655). We observed a higher prevalence of SS in patients with the diffuse form of SSc (p = 0,021). Table 3 shows the results for the cutaneous, vascular and musculoskeletal manifestations in SSc patients with SS present or absent. There was no association between clinical manifestations and the result (present or absent) for the SS in SSc patients (chi-square test, p value ranging between 0.216 and 0.951). There was also no significant difference between patients with SS present or absent in relation to skin score (t-student test, p = 0.816). The results related to gastrointestinal, cardiopulmonary and kidney manifestations in patients with SSc and SS present or absent, are shown in Table 4. There was no association between the presence and absence for the SS and the variables related to gastrointestinal, cardiopulmonary and kidney manifestations observed in patients evaluated in this study (chi-square test, p value ranging between 0.141 and 0.973). The results of the laboratory tests in SSc patients with SS present or absent are shown in Table 5. We found only differences in the percentage of patients who had SS present and positives anti-Ro (SSA) and anti-La (SSB), which were higher than those observed in patients with missing syndrome (0.0% - N = 0 - chi-square test, p = <0.001). For other laboratory tests, such as anti-Sm, anti RNP, Anti-Jo1, ESR, CRP, CPK, Cr, C3, C4 and hand Rx, there was no difference between patients with presence of the syndrome and those without the syndrome (student t test, p value ranging between 0.177 and 0.941). All patients with real overlap between SSc and SS had dry eye and dry mouth (100% - n = 16). Among patients only carriers of SSc evaluated in this study and who reported sicca symptoms, 66,7% had dry eye and 62,3% had dry mouth, reaching statistical significance (chi-square test, respectively p = 0.003 and p = 0.001). Data presented in Table 6.

Discussion

Sicca symptoms are common in patients with systemic sclerosis (68% - 71.2%), and usually explained by fibrosis of exocrine glands in patients with diffuse disease and extensive systemic involvement [3,10,11]. Association between SSc and decrease of lachrymal or salivary secretion is a relatively common finding [10,25]. We found similar rates to those described in the literature, with occurrence of dry eye in 66.7% and dry mouth in 62.3% of patients with SSc and sicca symptoms (with or without association with Sjögren). Kobak et al. [10] observed, as in this study, that sicca symptoms were found in all patients with SS and SSc overlapping, while the group of patients with SSc alone had a statistically significant lower frequency of dry eye and dry mouth. Drosos et al. [26] detected histopathological changes compatible with SS by biopsy of the labial salivary gland in 20.5% of the SSc patients, although in most cases the decrease in the secretory function is caused by submucosal fibrosis and "genuine" SS cannot be often present in SSc patients. In our case, there was predominance of SS in patients with the diffuse disease of SSc, but also in two patients with the limited form with long period of disease evolution. Maeshima et al. [25] describe that autoimmune diseases can be accompanied by dysfunction of the salivary glands regardless of the presence or absence of association with SS. The authors found salivary secretion disorders in 58.3% of patients with several diseases of connective tissue, excluding patients with primary SS. Among patients who did not have secondary association with SS, the SSc was the disease that most closely correlated with salivary dysfunction [25]. Corroborating these findings, this study observed a similar frequency of 62,3% of dry mouth in patients with SSc and without SS.

Variable	Sjögren's syndrome		p value
	Present	Absent	
Epidemiological data			
Age	52,25 ± 2,56	51,98 ± 1,71	0,938
Sex			
Male	0,0 (0)	1,9 (1)	0,578
Female	100,0 (16)	98,1 (52)	
Color			
White	31,3 (5)	52,8 (28)	0,197
Brown	56,3 (9)	43,4 (23)	
Black	12,4 (2)	3,8 (2)	
Time of disease			
Less than 5 years	18,8 (3)	26,4 (14)	0,655
Between 5 and 10 years	43,8 (7)	47,2 (25)	
More than 10 years	37,4 (6)	26,4 (14)	
Raynaud's phenomenon before diagnosis (years)	4,63 ± 2,18	3,96 ± 0,98	0,758
Disease duration after diagnosis	10,06 ± 1,48	9,36 ± 0,87	0,694
Clinical form			
Limited	12,5 (2)	49,1 (26)	0,021
Diffuse	75,0 (12)	28,3 (15)	
Early systemic sclerosis	0,0 (0)	13,2 (7)	
Overlap	12,5 (2)	9,4 (5)	
Monitoring index			
sHAQ	0,67 ± 0,09	0,61 ± 0,06	0,603
Medsger's Severity scale	5,06 ± 0,56	4,87 ± 0,41	0,811
Valentini's Activity scale	2,69 ± 0,26	2,36 ± 0,20	0,411

Results are presented as mean ± standard error of the mean or relative frequency (absolute frequency). * P value in the Student t test or chi-square test. sHAQ: Health Assessment Questionnaire in systemic sclerosis.

Table 2: Distribution of patients evaluated in this study and results of the epidemiological data and monitoring index in SSc patients with Sjögren's syndrome present or absent.

Variable	Sjögren's syndrome		p value
	Present	Absent	
Cutaneous manifestations			
Calcinosis			
Yes	40,0 (4)	17,0 (9)	0,723
No	60,0 (12)	83,0 (44)	
Hands			
Without changes	6,2 (1)	24,5 (13)	0,216
With changes	93,8 (15)	75,5 (40)	
Cutaneous involvement in hands (n=54)			
Puffy fingers	40,0 (6)	25,6 (10)	0,324
Indurative phase	40,0 (6)	33,3 (13)	
Atrophic stage	20,0 (3)	41,1 (16)	
Modified Rodnan's score	12,25 ± 1,39	12,77 ± 1,16	0,816
Vascular manifestations			
RP			
Objective	81,2 (13)	62,3 (33)	0,267
Subjective	18,8 (3)	37,7 (20)	
Micro scars			
Yes	18,8 (3)	22,6 (12)	0,741
No	81,2 (13)	77,4 (41)	
Active ulcers			
Yes	6,2 (1)	9,4 (5)	0,692
No	93,8 (15)	90,6 (48)	
Necrosis or finger amputation			
Yes	12,5 (2)	7,5 (4)	0,912
No	87,5 (14)	92,5 (49)	
Telangiectasia			
Yes	75,0 (12)	67,9 (36)	0,819
No	25,0 (4)	32,1 (17)	
Musculoskeletal manifestations			
Arthritis / synovitis			
Yes	50,0 (8)	32,1 (17)	0,312
No	50,0 (8)	67,9 (36)	
Contracture in flexion of hands			
Yes	6,2 (1)	13,2 (7)	0,752
No	93,8 (15)	86,8 (46)	
Tendon friction rubs			
Yes	6,2 (1)	1,9 (1)	0,951
No	93,8 (15)	98,1 (52)	
Muscle weakness			
Yes	40,0 (4)	11,3 (6)	0,339
No	60,0 (12)	88,7 (47)	
Muscle atrophy			
Yes	6,2 (1)	11,3 (6)	0,907
No	93,8 (15)	88,7 (47)	

Results are presented as mean ± standard error of the mean or relative frequency (absolute frequency). * P value in the Student t test or chi-square test. RP: Raynaud's phenomenon.

Table 3: Distribution of patients evaluated in this study and results for the cutaneous manifestations, vascular and musculoskeletal in SSc patients with Sjögren's syndrome present or absent.

However, only about 14 to 20% of patients meet diagnostic criteria for SS [3,11]. Published data about the true association between SS in SSc are extremely divergent and inconsistent. Perhaps the main reason for this discrepancy is the use of various criteria used for the diagnosis of SS in different studies [10]. We observed a prevalence of SS in 23.2% of patients with SSc, through the American-European Consensus Group on Classification Criteria for Sjögren's syndrome [14]. Another study found the prevalence of SS in 10.3% of 165 patients with SSc. In these patients the SS was the second most frequent overlap, accounting for 42.5% of all overlap syndromes [11].

In general, the SS was found more frequently in patients with the limited form of SSc, which was attributed to specific autoimmunity mediated by B lymphocytes with predominant production of anticentromere antibody [10]. However, in our study, vast majority of patients were both diffuse and limited form of the disease with long evolution time and two patients also had overlap with rheumatoid arthritis.

Variable	Sjögren's syndrome		p value
	Present	Absent	
Gastrointestinal manifestations			
Esophagus involvement			
Yes	81,3 (13)	69,8 (37)	0,563
No	18,8 (3)	30,2 (16)	
Other GI manifestations			
GERD	25,0 (4)	22,6 (12)	0,845
Esophagitis	31,3 (5)	20,8 (11)	0,593
Gastritis	31,3 (5)	22,6 (12)	0,712
Esophageal hypotonia	18,8 (3)	15,1 (8)	0,726
Esophageal dilatation	12,5 (2)	5,7 (3)	0,708
Cardiopulmonary manifestations			
FVC - classification			
>80%	50,0 (8)	56,6 (30)	0,796
Between 70 and 80%	31,3 (5)	32,1 (17)	
Between 50 and 69%	12,5 (2)	9,4 (5)	
<50%	6,3 (1)	1,9 (1)	
High resolution lung CT			
Normal	31,3 (5)	54,7 (29)	0,174
Abnormal	68,8 (11)	45,3 (24)	
Findings in CT (n=35)			
Fibrosis	63,6 (7)	70,8 (17)	0,973
"Ground glass" pattern	36,4 (4)	29,2 (7)	
Eco PSAP	39,50 ± 4,57	32,83 ± 3,42	0,325
Echocardiogram			
Normal	71,4 (9)	45,3 (24)	0,628
Abnormal	28,6 (7)	54,7 (29)	
Findings in echocardiography (n=31)			
Valvulopathy	31,3 (5)	26,4 (14)	0,952
Concentric LVH	0,0 (0)	18,9 (10)	0,141
LV diastolic dysfunction	12,5 (2)	15,1 (8)	0,796
PAH mild or moderate	18,8 (3)	11,3 (6)	0,727
Pericarditis	18,8 (3)	7,5 (4)	0,407
Renal manifestations			
Renal crisis			
Yes	0,0 (0)	1,9 (1)	0,580
No	100,0 (16)	98,1 (52)	

Results are presented as mean ± standard error of the mean or relative frequency (absolute frequency). * P value in the Student t test or chi-square test. GI: gastrointestinal; GERD: Gastroesophageal reflux disease; FVC: pulmonary functional vital capacity; Eco PSAP: estimated pulmonary artery pressure by transthoracic echocardiography; LVH: left ventricular hypertrophy; LV: left ventricle; PAH: pulmonary arterial hypertension.

Table 4: Results related to gastrointestinal, cardiopulmonary and renal manifestations in SSc patients with Sjögren's syndrome present or absent.

Variable	Sjögren's syndrome		p value
	Present	Absent	
ESR	34,94 ± 6,13	26,57 ± 2,82	0,177
CRP	13,92 ± 4,34	12,04 ± 2,96	0,751
CPK	136,06 ± 42,81	130,64 ± 14,73	0,879
Creatinine	0,74 ± 0,03	0,75 ± 0,03	0,894
C3	125,88 ± 7,19	132,23 ± 3,65	0,414
C4	31,44 ± 2,56	34,26 ± 1,30	0,308
Anti-Ro			
Positive	68,8 (11)[a]	0,0 (0)[b]	<0,001
Negative	31,3 (5)[b]	100,0 (53)[a]	
Anti-La			
Positive	37,5 (6)[a]	0,0 (0)[b]	<0,001
Negative	62,5 (10)[b]	100,0 (53)[a]	
Anti-Sm			
Positive	0,0 (0)	1,9 (1)	0,580
Negative	100,0 (16)	98,1 (52)	
Anti-RNP			
Positive	12,5 (2)	13,2 (7)	0,941
Negative	87,5 (14)	86,8 (46)	
Anti-Jo 1			
Positive	6,3 (1)	3,8 (2)	0,670
Negative	93,8 (15)	96,2 (51)	
Hands X-rays			
Normal	37,5 (6)	60,4 (32)	0,185
Abnormal	62,5 (10)	39,6 (21)	
Findings on hands X-rays (n=31)			
Calcinosis	60,0 (6)	38,1 (8)	0,448
Resorption (distal phalange)	40,0 (4)	61,9 (13)	

Results are presented as mean ± standard error of the mean or relative frequency (absolute frequency). * P value in the Student t test or chi-square test. Different letters on the line indicate significant differences between patients with and without Sjögren's syndrome (chi-square test, p <0.05). ESR: erythrocyte sedimentation rate; CRP: C reactive protein; CPK: creatine phosphokinase; C3: C3 fraction of the complement; C4: fraction of complement C4; X-rays: radiography.

Table 5: Other results of the laboratory tests in SSc patients with Sjögren's syndrome present or absent.

Symptom	Sjögren's syndrome		p value	Total
	Present	Absent		
Dry mouth				
Yes	100,0 (16)[a]	50,9 (27)[b]	0,001	62,3 (43)
No	0,0 (0)[b]	49,1 (26)[a]		37,7 (26)
Total	23,2 (16)	76,8 (53)		100,0 (69)
Dry eyes				
Yes	100,0 (16)[a]	56,6 (40)	0,003	66,7 (46)
No	0,0 (0)[b]	43,4 (23)		33,3 (23)
Total	23,2 (16)	76,8 (53)		100,0 (69)

The results are presented as relative frequency (absolute frequency). * P value in the Student t test or chi-square test. Different letters on the line indicate significant differences between patients with and without Sjögren's syndrome (chi-square test, p <0.05).

Table 6: Distribution of SSc patients evaluated in this study, according to the association with Sjögren's syndrome and the presence of xerostomia or xerophthalmia.

Several cases of overlap between SSc, SS and other autoimmune diseases are reported in the literature [27], including patient with anti synthetase syndrome with positivity for anti isoleucyl-tRNA synthetase (anti-OJ antibody), with severe systemic involvement and pulmonary, esophageal, skin, muscle and microvascular impairment [28]. However all of our patients with SSc and SS were negative for antibodies to anti synthetase syndrome (anti-Jo1) and anti-OJ was not dosed in our research. Many are also the cases of association between SS, SSc particularly of the limited subtype CREST (calcinosis, Raynaud, esophageal dysmotility, sclerodactyly, and telangiectasia) and primary biliary cirrhosis (PBC), sometimes also increased autoimmune thyroiditis [27,29,30]. Furthermore already been reported patient case with SS, SSc and idiopathic portal hypertension without hepatic cirrhosis [31]. These similar results suggest that the association between these autoimmune diseases is not merely accidental, but share immunological abnormalities including production of autoantibodies [29]. Salliot et al. [9] highlight that the association of SS with SSc reflects the dissemination of autoimmunity, since a third autoimmune disorder (primary biliary cirrhosis - PBC) was present in 40% of cases. For example, the high incidence of patients with PBC in SS can be partially explained by the presence of a common antigen in bile ductal epithelium, and salivary gland [29]. Still the Mayo Clinic study evaluating 113 patients with PBC, found that 84% of patients had at least one other autoimmune disorder, 18% of those with SSc [27]. But none of our patients presented PBC.

A rare association of patients with SSc and SS overlapping associated with psoriasis vulgaris has been described in the literature [32]. The association between psoriasis and SSc was already rare, with total of 13 patients reported in the literature [32]. In this case also we did not observe this association in our patients.

Other factors that can generate diagnostic confusion are due to reports of a subgroup of patients with primary SS and positive anti-centromere antibodies (ACA), recognized as having intermediate characteristics between SS and SSc [7,9]. The prevalence of ACA in patients with primary SS is conflicting, with initial reports reporting frequency between 16-27% and most recent publications found lower prevalence, between 2-7% [6]. However, only about one quarter of patients who initially presented with these characteristics may be developed SSc, despite a long period of follow-up [3,8].

Although only 43.8% of our patients with SSc and SS had positive ACA, the literature suggests that dosing this antibody in patients with primary SS and Raynaud's phenomenon, since these patients may have limited coexistence with SSc in limited form [3].

In these patients with SS and positive ACA, the sicca manifestations were observed in variable incidence from 13.6% to 37% and one of the studies demonstrated infiltration of mononuclear cells in minor salivary gland biopsies without fibrotic changes, probably related solely to the SS [5]. Wonders whether these patients with SS and positive results for ACA merely represent a subgroup of patients with SS or a transitional phase for evolving the SSc [8]. It was previously reported that the phenotype of various autoimmune diseases may be altered in those patients associated with SS [10]. Baldini et al. [7] emphasize that this subgroup of patients with SS and SSc overlap with positive ACA exhibit mild clinical involvement, with less cardiovascular, gastrointestinal and pulmonary fibrosis involvement, although a greater risk of non-Hodgkin's lymphoma development [6,7,33]. None of our patients with SS and SSc developed lymphoma in this short period of observation. Indeed, in the literature there is a general agreement that in patients with overlap syndrome, SSc is generally less severe while the glandular manifestations of SS tend to be fully manifest [3 4,6,7,9-11]. In other words, secondary or associated SS seems to have a favorable impact on the prognosis of patients with SSc. Kobak et al. [10] found in the patient group with overlap between SS and SSc a lower frequency of

fibrosis and pulmonary hypertension. Salliot et al. [9] found in the patient group with overlapping the same milder symptoms, and lower frequency of scleroderma renal crisis. However, it was not possible to observe a statistically lower incidence of arthritis, vascular disease, gastrointestinal, renal or pulmonary involvement in our patients.

Bournia et al. [7] concluded that patients with SS with ACA-positive represent a subset of patients with an intermediate phenotype between primary SS and SSc, with a slight tendency to evolve SSc. García-Carrasco et al. [34] found the presence of Raynaud's phenomenon in 13% of patients with primary SS, in this patient group attracted attention to a higher incidence of extra glandular manifestations such as arthritis and vasculitis, as well as autoantibodies (anti-Ro and anti -La) [34]. Especially, some patients with primary SS with positive ACA, showed changes in the nailfold capillaroscopy, although no clinical evidence of association with SSc. Accordingly, we observed that Raynaud's phenomenon was a prevalent and important manifestation in our patients with SSc and SS, as was observed in 81.3% of these patients, against 62.3% of patients with SSc alone. Previous findings suggest that the meeting of anti-Ro and anti-La autoantibodies may be specific serological markers of SS overlay in SSc patients [10]. We found anti-Ro in 68.8% of patients with SSc and SS, already the anti-La was observed in 37.5% of patients with the overlap. However, low titers of this antibody did not change the severity of arthritis, neuropathy or cryoglobulinemia in patients with SSc associated to SS [11]. Although there are still no reliable markers of overlap between SSc and SS is consensus in the literature the usefulness of anti-Ro and anti-La [10,11]. And in an early SSc stage, Wuttge et al. [35] suggest that a very high activity type I interferon would be related to the development of overlap syndromes in these patients, such as SS and lupus, with formation of antibodies against extractable core antigens (Ro and La), immunoglobulin G and cytopenias elevation.

Conclusion

We conclude that the presence of SS did not affect positively or negatively the severity or the clinical manifestations observed in patients with SSc. We observed a prevalence of SS in 23.2% of patients with SSc, mainly in patients of diffuse form of the disease, the principal clinical manifestation [4-6,8] was the Raynaud's phenomenon, and positivity for antibodies against extractable core antigens (Ro and La). The sicca symptoms were very common in this study, occurring in 66.7% of dry eye, and dry mouth in 62.3% of all patients with SSc.

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