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# Sjögren's syndrome: An underdiagnosed condition in mixed connective tissue disease

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**OBJECTIVE:** To determine the prevalence of sicca symptoms, dry eye, and secondary Sjögren's syndrome and to evaluate the severity of dry eye in patients with mixed connective tissue disease.

**METHODS:** In total, 44 consecutive patients with mixed connective tissue disease (Kasukawa's criteria) and 41 healthy controls underwent Schirmer's test, a tear film breakup time test, and ocular surface staining to investigate dry eye. In addition, the dry eye severity was graded. Ocular and oral symptoms were assessed using a structured questionnaire. Salivary gland scintigraphy was performed in all patients. Classification of secondary Sjögren's syndrome was assessed according to the American-European Consensus Group criteria.

**RESULTS:** The patients and controls had comparable ages (44.7 ± 12.4 *vs.* 47.2 ± 12.2 years) and frequencies of female gender (93 *vs.* 95%) and Caucasian ethnicity (71.4 *vs.* 85%). Ocular symptoms (47.7 *vs.* 24.4%) and oral symptoms (52.3 *vs.* 9.7%) were significantly more frequent in patients than in controls. Fourteen (31.8%) patients fulfilled Sjögren's syndrome criteria, seven of whom (50%) did not have this diagnosis prior to study inclusion. A further comparison of patients with mixed connective tissue disease with or without Sjögren's syndrome revealed that the former presented significantly lower frequencies of polyarthritis and cutaneous involvement than did the patients without Sjögren's syndrome. Moderate to severe dry eye was found in 13 of 14 patients with mixed connective tissue disease and Sjögren's syndrome (92.8%).

**CONCLUSIONS:** Sjögren's syndrome, particularly with moderate to severe dry eye, is frequent in patients with mixed connective tissue disease. These findings alert the physician regarding the importance of the appropriate diagnosis of this syndrome in such patients.

**KEYWORDS:** Mixed Connective Tissue Disease; Sjögren's Syndrome; Dry Eye; Dry Mouth; Anti-Ro/SSA.

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## INTRODUCTION

Mixed connective tissue disease (MCTD) is an inflammatory disease characterized by combined features of systemic lupus erythematosus (SLE), systemic sclerosis (SSc), and polymyositis (PM) that is associated with high serum titers of antibody to extractable nuclear antigen, with a specificity for nuclear ribonucleoprotein (1). The large spectrum of clinical signs and symptoms of MCTD includes sicca symptoms and Sjögren's syndrome (SS). However, the actual frequencies of dry eye and SS in MCTD patients are poorly characterized (2,3).

Dry eye, or keratoconjunctivitis sicca, is a multifactorial condition that affects the tear film and ocular surface due to abnormalities in the quality or quantity of the tear film. This condition is accompanied by an increase in the film's osmolarity and inflammation of the ocular surface (4). Dry eye is commonly observed in systemic autoimmune disorders, such as primary SS (pSS), rheumatoid arthritis (RA), SLE, and SSc (4-6). This condition is characterized by symptoms of ocular irritation and discomfort, which affect functional visual acuity and the ability to work, read, use a computer, and drive at night (7,8). Dry eye also increases the risk of eye infection and destruction of ocular tissue (9). Millions of people worldwide suffer from dry eye, and currently, recognition of the magnitude of the disease and knowledge of its pathogenesis and treatment are changing (9-12).

SS affects exocrine glands by lymphocytic infiltration, causing stomatitis and dry eye (13). SS may occur alone as



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pSS or may accompany other autoimmune disorders as secondary SS (14). Data regarding dry eye and secondary SS in MCTD are scarce in the literature, with a prevalence ranging from 14.5 to 56% (3,15). The few available studies were retrospective, without a control group or strict exclusion criteria (1-3,16,17), precluding a definitive conclusion about their findings. In addition, there are no data regarding the severity of dry eye according to established criteria in MCTD patients. These aspects are important because dry eye and SS may have a significant impact on the quality of life and treatment of MCTD patients.

The aim of this study was therefore to determine the prevalence of sicca symptoms, dry eye, and secondary SS and to evaluate the severity of dry eye in MCTD patients.

## PATIENTS AND METHODS

### Patients

This cross-sectional study included 44 consecutive patients with MCTD who were followed at the Rheumatology Division of the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo. This tertiary referral hospital is linked to a university center. All patients fulfilled the MCTD classification criteria of Kasukawa et al. (18), with at least one of the following common symptoms: 1) Raynaud's phenomenon or swollen fingers or hands; 2) the presence of anti-U1RNP; and 3) one or more findings in at least two of three categories, including SLE-like (polyarthritis, pericarditis/pleuritis, lymphadenopathy, facial erythema, and leukopenia/thrombocytopenia), scleroderma-like (sclerodactyly, pulmonary fibrosis, and esophageal dysmotility), and polymyositis-like (muscle weakness, high creatine phosphokinase levels and myopathic electroneuromyography). The patients tested persistently negative for anti-dsDNA and anti-Sm antibodies. Patients with a history of current use of xerogenic drugs, head and neck radiation treatment, hepatitis B/C, acquired immunodeficiency syndrome (AIDS), preexisting lymphoma, sarcoidosis, or graft-versus-host disease were not included (19). In addition, smokers and patients receiving hormonal replacement therapy were excluded.

### Controls

In total, 41 healthy volunteer controls with a comparable mean age and gender distribution and with the same exclusion criteria were evaluated for dry eye. The local research ethics committee approved the study, and informed consent was obtained from all patients and controls.

### Clinical and laboratorial data

A general evaluation collected data on age, gender, race, disease duration, and medications in current use (oral prednisone and/or cytotoxic drugs). The clinical aspects of MCTD that were evaluated were a SD-pattern in nailfold capillaroscopy, hypergammaglobulinemia (gammaglobulin>1.6 g/dl), esophageal involvement (determined by high-resolution computerized tomography or an esophagram), polyarthritis (arthritis involving five or more peripheral joints), muscle disease (muscle weakness associated with an elevation of creatine phosphokinase and/or aldolase levels in the absence of thyroid disease, infections or myopathy-inducing drugs) and cutaneous disease (SLE manifestation of malar rash or photosensitivity or SSc manifestation of sclerodactyly). Demographic and clinical/laboratorial features, including a previous diagnosis of SS, were obtained from the ongoing electronic database at 1- to 6-month intervals for 128 MCTD patients followed by our Rheumatology Division since 2001.

A questionnaire regarding ocular and oral symptoms according to the American-European Consensus Group classification criteria for SS was applied (AECG) (19). Sicca symptoms were defined as the presence of ocular dryness (daily persistent dry eyes, a recurrent sensation of sand and gravel in the eyes, and/or the use of tear substitutes more than three times per day) and oral dryness (a daily feeling of dry mouth, recurrent or persistently swollen salivary glands, and/or frequent drinking of liquids to aid in swallowing dry food) (19).

Salivary gland scintigraphy was performed in all MCTD patients to investigate salivary concentration and secretion abnormalities. A serologic evaluation examined the expression of rheumatoid factor (by latex fixation assay) and anti-Ro/SSA and anti-La/SSB antibodies (by counterimmunoelectrophoresis), as previously described (20,21).

An ophthalmic evaluation performed at the Ophthalmologic Department of Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo included the following: Schirmer's I test without anesthetic to evaluate aqueous tear production, a tear breakup time (BUT) test to measure tear film stability, and tests for the evaluation of epithelial ocular surface integrity by diagnostic dyes. These dyes included a fluorescein 1% eyedrop for the corneal area and a rose bengal 1% eyedrop for the conjunctiva. The cornea was divided into three areas (superior, central, and inferior), and each area's staining with the fluorescein dye was scored from 0 to 3 (with the total ranging from 0 to 9) if epitheliopathy was present. The conjunctiva was also divided into three areas (nasal, central, and temporal), whose staining with the rose bengal eyedrop was assessed using the same score as for fluorescein. All MCTD patients and volunteer controls were examined under the same conditions of room temperature and humidity (medians 21.5℃ and 65%, respectively) (4,5).

Dry eye severity was classified using the grading scheme of Behrens et al. (6), based on scoring of symptoms and clinical signs. The levels of severity ranged from 1 to 4: level 1 (mild): mild symptoms, no conjunctival or corneal staining and variable values of BUT (sec) and on Schirmer's test (mm/5 min); level 2 (moderate): moderate symptoms, variable scores for conjunctival and corneal staining, a BUT ≤10 sec and Schirmer's test score ≤10 mm/5 min; level 3 (moderate/severe): severe or frequent symptoms, moderate to marked conjunctival and corneal staining, a BUT ≤5 sec and Schirmer's test score ≤5 mm/5 min; and level 4 (severe): severe symptoms, severe conjunctival and corneal staining, immediate BUT and Schirmer's test score ≤2 mm/5 min.

The revised AECG criteria for SS were applied. The presence of item I (ocular symptoms) or item II (oral symptoms) plus items III (objective evidence of ocular involvement) and V (objective evidence of salivary gland involvement) is considered to be indicative of secondary SS (19). It is noteworthy that to be classified as having secondary SS, patients must present ocular or oral symptoms and ocular and oral objective signs (19).

### Statistical analysis

The results are presented as the mean and standard deviation for continuous variables and as the frequency (%)

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for categorical variables. To evaluate differences between patients and controls, for continuous variables, we used a t test or Mann-Whitney test. For categorical variables, differences were assessed by a chi-square test or Fisher's exact test. Dunn's test and a Kruskal-Wallis test were used for nonparametric test data. The McNemar symmetry test was applied to evaluate patients diagnosed with secondary SS according to the AECG criteria and to compare them to the group of patients who had a previous SS diagnosis. Values were considered statistically significant when $p<0.05$.

## RESULTS

### Demographic features of MCTD patients and controls

The MCTD patients and controls were of a similar age (44.7±12.4 [range 22 to 67 years] *vs.* 47.2±12.2 [range 23 to 70 years] years; $p=0.3$) and presented similar frequencies of female gender (93 *vs.* 95%; $p=1.0$) and Caucasian ethnicity (71.4 *vs.* 85%; $p=0.1$).

### Clinical and therapeutic features of MCTD patients

The mean disease duration was 10.8±7.3 years (range 2 to 35 years). Sixteen (36.4%) patients were using cytotoxic drugs (azathioprine, cyclophosphamide, or methotrexate), and 10 (22.7%) patients were receiving high dosages of oral prednisone (>20 mg per day). Serum anti-Ro/SSA antibodies were detected in 29.5% of patients, whereas only 1 (2.3%) had a positive result for anti-La/SSB antibodies. Rheumatoid factor was positive in 18 of 44 (40.9%) patients.

### Sicca symptoms

In total, 21 (47.7%) patients had at least one ocular symptom of dry eye (item I of the AECG criteria for SS). Of these patients, 20 (45.5%) patients had daily and persistently troublesome dry eyes for more than 3 months, and 8 (18.2%) patients had a recurrent sensation of sand or gravel in their eyes. The same percentage of patients used tear substitutes more than three times per day (Table 1).

Concerning oral symptoms, 23 (52.3%) patients presented at least one positive symptom for dry mouth (item II of the AECG criteria for SS). Of these patients, 22 (50%) patients had a daily feeling of dry mouth for more than 3 months, and 8 (18.2%) patients had recurrent or persistent swollen salivary glands as an adult. Additionally, 12 (27.3%) patients frequently drank liquids to aid in swallowing dry foods.

Sicca symptoms (dry eye and dry mouth) were present in 17 (38.6%) patients (Table 1). Symptoms of dry eye (47.7 *vs.* 24.4%) and dry mouth (52.3 *vs.* 9.7%) were significantly more frequent in patients than in controls ($p=0.02$ and $p=0.001$, respectively).

### Ocular and oral involvement

There was objective evidence of ocular involvement (Schirmer's I test ≤5 mm/5 min or rose bengal staining score ≥4) in 52.3% of patients (Schirmer's I test ≤5 mm/5 min was positive in 43.2% of patients, and a rose bengal staining score ≥4 was observed in 27.3% of patients) (Table 1).

Objective evidence of salivary gland involvement, as determined by scintigraphy (item V), was positive in 70.4% of MCTD patients.

**Table 1 -** Sicca symptoms and dry eye evaluation in MCTD patients and controls.

| | MCTD (n = 44) | Control (n = 41) | *p*-value |
|---|---|---|---|
| Ocular symptoms (%) | 21 (47.7) | 10 (24.4) | 0.02 |
| Oral symptoms (%) | 23 (52.3) | 4 (9.7) | 0.001 |
| Ocular+oral symptoms (%) | 17 (38.6) | 4 (9.7) | 0.002 |
| **Schirmer's test** | | | |
| ≤5 mm/5 min; n (%) | 19 (43.2) | 3 (7.3) | 0.001 |
| Mean ± SD (mm/5 min) | 10.5±8.8 | 22.9±11.0 | 0.001 |
| **BUT** | | | |
| <10 sec; n (%) | 35 (79.5) | 29 (70.7) | 0.3 |
| Mean ± SD (sec) | 7.7±3.3 | 9.3±5.4 | 0.05 |
| **Fluorescein** | | | |
| ≥4 score; n (%) | 12 (27.3) | 0 (0) | 0.08 |
| Mean ± SD (score) | 0.7±0.8 | 0.07±0.26 | 0.001 |
| **Rose bengal** | | | |
| ≥4 score; n (%) | 12 (27.3) | 0 (0) | 0.001 |
| Mean ± SD (score) | 2.8±2.3 | 0.1±0.2 | 0.001 |

Sicca symptoms: ocular and oral symptoms. MCTD: mixed connective tissue disease. *p*-value<0.05.

According to the dry eye severity grading scheme, 19 of 44 (43.2%) MCTD patients had level 1 (mild), 12 of 44 (27.3%) had level 2 (moderate), 4 of 44 (9.1%) had level 3 (moderate/severe), and 3 of 44 (6.8%) had level 4 (severe) of severity (Table 2). In the control group, there was only 1 (2.4%) person with moderate dry eye (level 2), and 12 (29.3%) presented mild dry eye (level 1) (Table 2). All diagnostic dry eye tests performed in MCTD patients presented mean ± standard deviation values that were significantly different from those of the control group (Table 1).

### Sjögren's syndrome

The frequency of secondary SS according to the revised AECG classification criteria was 31.8% of MCTD patients (n = 14), and 7 (50%) did not have this diagnosis prior to study inclusion ($p<0.001$). Moderate to severe dry eye was found in 13 of 14 patients with SS (92.8%). Concerning non-SS patients (n = 30), 80% of patients had dry eye (63.3% with mild dry eye and 16.7% with moderate dry eye).

**Table 2 -** Severity grading of dry eyes in MCTD patients and controls.

| | MCTD (n = 44) | Control (n = 41) | *p*-value |
|---|---|---|---|
| **Moderate/severe** n **(%)** | 19 (43.2) | 1 (2.4) | |
| Schirmer's test (mm/5 min) | 5.9±4.6 | 8.0 | NA |
| BUT (sec) | 7.1±2.7 | 7.0 | NA |
| Fluorescein (score) | 1.1±0.9 | 1.0 | NA |
| Rose bengal (score) | 4.1±2.5 | 1.0 | NA |
| **Mild** n (%) | 19 (43.2) | 12 (29.3) | |
| Schirmer's test (mm/5 min) | 12.0±8.9 | 16.9±11.8 | 0.2 |
| BUT (sec) | 6.7±3.7 | 7.5±5.3 | 0.8 |
| Fluorescein (score) | 0.3±0.6 | 0.1±0.3 | 0.1 |
| Rose bengal (score) | 2.3±1.6 | 0.2±0.4 | 0.001 |
| **Normal** n (%) | 6 (13.6) | 28 (68.3) | |
| Schirmer's test (mm/5 min) | 20.0±10.5 | 26.0±9.4 | 0.2 |
| BUT (sec) | 9.7±3.4 | 10.3±5.4 | 1.0 |
| Fluorescein (score) | 0.2±0.4 | 0.1±0.2 | 0.2 |
| Rose bengal (score) | 0.7±0.5 | 0.0±0.0 | 0.001 |

MCTD: mixed connective tissue disease; BUT: breakup time. Moderate/severe dry eye = levels 2, 3, and 4; mild dry eye = level 1; normal = without dry eye. The values are expressed as the mean ± standard deviation. *p*-value<0.05. NA: not available (n = 1 in control group).

A further comparative analysis of MCTD patients with and without SS revealed that polyarthritis (64.3 *vs*. 93.3%, $p = 0.02$) and cutaneous disease (35.7 *vs*. 70.0%, $p = 0.03$) were less frequent in patients with SS (Table 3). Disease duration, age, esophageal involvement, muscle disease, SD-pattern in nailfold capillaroscopy, hypergammaglobulinemia, anti-Ro/SSA expression, anti-La/SSB expression, and rheumatoid factor expression were similar in MCTD patients with and without SS. The use of prednisone at a dosage above 20 mg/day and of cytotoxic drugs did not differ between the two groups (Table 3).

## DISCUSSION

In the present study, the authors identified dry eye, sicca symptoms, and SS as frequently associated conditions in MCTD patients.

The prevalence of dry eye in the normal population is generally 5% to 17% (10). In the present study, approximately half of MCTD patients had this condition, with a frequency similar to frequencies reported in SLE (31% to 76%) and SSc (38% to 81%) (1,22-24). Importantly, we used strict selection criteria for MCTD (18), and the inclusion of an age- and gender-matched healthy control group improved the accuracy of our findings because these factors strongly influence the frequencies of sicca symptoms and dry eye (8).

Data from this study also allowed the classification of dry eye severity (6) because a thorough investigation of this condition was performed, including the application of a standardized sicca syndrome questionnaire (19). In addition, the use of the severity grading scheme, which included both symptoms and objective findings (clinical evaluation and diagnostic tests), increased the frequency of dry eye diagnosis (86.4%) compared with the assessment of ocular symptoms (47.7%) or objective evidence of ocular involvement (52.3%) alone, most likely yielding a better diagnostic accuracy than clinical and objective evaluations together (19). In this regard, we emphasize that dry eye has an important impact on the ability to perform daily activities, even in mild to moderate cases (25). This is the first study in the literature that has applied severity criteria to patients with MCTD. Furthermore, dry eye severity grading has not been reported for other rheumatic autoimmune diseases, such as SLE and SSc (26,27). Our findings show that moderate to severe dry eye is frequent in MCTD patients and indicate the importance of making this diagnosis in MCTD patients so that a therapeutic strategy can be established, which may improve the conditions of the ocular surface, consequently reducing morbidity due to dry eye (9,28).

In this study, we applied rigorous exclusion criteria, such as the exclusion of smoking, estrogen replacement therapy, and the use of xerogenic medications, to rule out environmental factors and other risk factors known to be associated with dry eye (8,28-31). Therefore, our findings demonstrate the important role of MCTD itself in the development of dry eye, suggesting the possibility that the ocular surface and the main lacrimal gland could be target organs in the MCTD autoimmune process (18,32).

Regarding sicca symptoms, our finding (38.6%) is comparable with the prevalence range reported previously (3,16,33), although score values for both tests were not consistently provided by authors (16). Ohtsuka et al. retrospectively investigated salivary gland involvement by sialography and found sialectasia in 82.1% of patients, but they did not investigate sicca symptoms and reported the prevalence of secondary SS to be 56.4%. The authors defined this condition by the simultaneous presence of abnormal sialography and clinical dry eyes (Schirmer's I test<10 mm/5min) or dry mouth (salivary gland secretion following citric acid stimulation <10 ml/5 min) (15). Setty et al. found that 42% of MCTD patients had sicca symptoms. However, their study was retrospective, and the authors defined sicca symptoms as daily dryness, frequent use of liquids due to oral dryness, and daily ocular dryness and did not evaluate objective ocular or oral involvement (3).

Currently, there is a trend that involves using the term ''associated SS'' instead of ''secondary SS''. However, patients with other concomitant diffuse connective tissue diseases, such as MCTD, are labeled by the revised AECG criteria as having SS (19), and in these criteria, SS is classified as primary or secondary. Thus, this designation was applied in the present study. In this regard, according to the definition of secondary SS established by the revised classification criteria of the AECG (19), we observed that nearly one-third of MCTD patients had SS. Indeed, this is the first study applying the AECG criteria to evaluate the prevalence of secondary SS in a population of MCTD patients. The present evaluation also reveals that SS is often underdiagnosed in MCTD. Efforts should be made to ensure that this condition is not neglected because it induces a chronic disability and is an important factor to consider when planning treatment interventions and improvement of the quality of a patient's life (34). This importance is evidenced

**Table 3 -** Clinical features of MCTD patients with and without secondary SS.

| | SS n = 14 | Non-SS n = 30 | *p*-value |
|---|---|---|---|
| Disease duration (years) | 13.0±7.1 | 9.8±7.2 | 0.11 |
| Age (years) | 48.6±11.9 | 42.8±12.4 | 0.15 |
| Cytotoxic drugs (%) | 4 (28.6) | 12 (40) | 0.4 |
| Prednisone >20 mg/day (%) | 3 (21.4) | 7 (23.3) | 1.00 |
| SD-pattern in nailfold capillaroscopy (%) | 5 (35.7) | 15 (50) | 0.43 |
| Hypergammaglobulinemia (%) | 13 (92.8) | 23 (76.7) | 0.40 |
| Esophageal involvement (%) | 11 (78.6) | 23 (76.7) | 1.00 |
| Polyarthritis (%) | 9 (64.3) | 28 (93.3) | 0.02 |
| Muscle disease (%) | 5 (35.7) | 12 (40) | 0.78 |
| Cutaneous disease (%) | 5 (35.7) | 21 (70) | 0.03 |
| Anti-Ro/SSA (%) | 5 (35.7) | 8 (26.7) | 0.72 |
| Anti-La/SSB (%) | 0 (0) | 1 (3.3) | 1.00 |
| Positive rheumatoid factor (%) | 7 (50) | 11 (36.7) | 0.42 |

MCTD: mixed connective tissue disease. *p*-value<0.05.

by the moderate to severe dry eye frequently found in these patients (92.8% in the SS group and 16.7% in the non-SS group in comparison with 2.4% in the control group).

A limitation of our study is the lack of minor salivary gland-related histological data. These data could perhaps increase the rate of diagnosis of SS in MCTD, in addition to enabling the study of possible correlations between the intensity of the inflammatory infiltrate in salivary glands and the intensity of sicca symptoms (19).

Interestingly, the presence of SS was associated with a lower prevalence of cutaneous and articular manifestations in MCTD patients, suggesting that MCTD patients with SS could have a distinct course of the underlying disease compared with non-SS MCTD patients, similar to what has been reported in SLE (35). However, this finding needs to be confirmed in future prospective studies.

In conclusion, SS is a frequently underdiagnosed condition associated with MCTD. Moderate to severe dry eye was found in the majority of patients with SS. These data justify the need for a systematic investigation of the exocrine glands in MCTD to achieve early diagnosis and to develop a treatment for improving the quality of life of patients.

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## ■ AUTHOR CONTRIBUTIONS

Usuba FS examined all patients, obtained the ethics approval, and wrote and submitted the manuscript. Lopes JB recruited and examined all patients. Fuller R and Alves MR designed and wrote the manuscript. Yamamoto JH wrote the manuscript. Pasoto SG directed the research and wrote the manuscript. Caleiro MT directed the research.

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