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ORIGINAL ARTICLE

Association of focus score and extraglandular involvement in Sjögren's syndrome: A study on antinuclear antibodies and minor salivary gland pathology

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ABSTRACT

Objectives: This study aimed to investigate the relationship between patients with and without extraglandular involvement in Sjögren's syndrome (SS) by analyzing ANA (antinuclear antibody) and ENA (extractable nuclear antigen) results and minor salivary gland pathology findings.

Patients and methods: A total of 265 (245 females; 20 males; mean age: 50.4±12.4; range, 19 to 79 years) patients diagnosed with SS were included in the retrospective cohort study between March 1, 2011, and December 1, 2021. Detailed documentation was performed, capturing demographic characteristics, clinical information, laboratory findings, medication usage, and manifestations of the syndrome. The patients were divided into two groups, with (78 females; 8 males; mean age: 52.7±11.5; range, 22 to 78 years or without (167 females; 12 males; mean age: 49.3±12.8; range, 19 to 79 years extraglandular involvement.

Results: The mean follow-up duration was 63.1±31.9 months. Extraganular involvement, including joint involvement, lung involvement, central nervous system involvement, hematological involvement, hepatitis, and lymphoma, was observed in 32.5% of the patients. Patients with extraglandular involvement required multiple medications, while those with only glandular involvement predominantly used hydroxychloroquine. The mean duration from SS diagnosis to extraglandular involvement was 15.2±27.8 months. The comparison between patients with and without extraglandular involvement revealed a significant association between higher focus scores (FS) and extraglandular manifestations. However, no significant differences were observed in terms of ANA positivity, ANA titers, or ENA positivity. Regression analysis indicated that age and FS were linked to systemic involvement.

Conclusion: This study highlights the importance of FS as a predictive indicator for extraglandular manifestations in SS. Advanced age was found to be associated with an increased likelihood of extraglandular involvement. Assessing FS and age can aid in predicting extraglandular manifestations.

Keywords: Antinuclear antibodies, extraglandular involvement, focus score, Sjögren's syndrome, systemic manifestations.

Sjögren's syndrome (SS) is a chronic, multisystem autoimmune disease characterized by inflammation of the salivary glands. The disease primarily manifests in the oral (xerostomia) and ocular (xerophthalmia) regions due to decreased or absent glandular secretions caused by autoimmune glandular involvement. It is also linked to various extraglandular symptoms. This condition, sometimes referred to as autoimmune epithelitis in certain academic circles, may present independently or in conjunction with other autoimmune disorders.[1]

Anti-Ro/SSA and anti-La/SSB antibodies can be detected in approximately 60 to 80% of individuals with SS. Antinuclear antibodies (ANA) are found in 90% of patients. Autoantibodies can be positive many years prior to the clinical onset of SS.[2] The salivary and lacrimal glands in individuals with SS are primarily characterized by the infiltration of lymphocytes, which constitutes the main pathological lesion. The infiltrates consist of focal clusters of lymphocytes that start around the ducts and extend to involve the entire lobule.

The severity of the disease determines the cellular composition of these infiltrations, resulting in varying patterns. T cells, especially $CD4^+$ cells, dominate in milder infiltrates that better resemble the gland's architecture. With the progression of SS, there is an increased predominance of B cells in larger and more intense infiltrates, which are correlated with acinar destruction and the loss of tissue structure.[3]

In patients with mild SS who have only sicca symptoms without glandular enlargement or involvement of other organs, treatment generally does not require systemic therapy apart from local treatment for ocular, oral, and other dryness symptoms. The management of individuals with moderate to severe involvement in SS depends on the clinical presentation and the specific tissues and organ systems affected. It encompasses systemic medical treatment, which may involve the administration of immunosuppressants and biological agents. The treatment strategies for SS have been influenced by the approaches utilized for other systemic rheumatic diseases, specifically systemic lupus erythematosus and rheumatoid arthritis. The treatment of SS involves the use of topical and systemic glucocorticoids, hydroxychloroquine, methotrexate, azathioprine, mycophenolate, and agents such as rituximab, depending on the type of involvement of the disease.[4-6]

This study aimed to establish the correlation between individuals with extraglandular manifestations in SS and those without such manifestations, utilizing ANA and ENA (extractable nuclear antigen) results and minor salivary gland pathology findings.

PATIENTS AND METHODS

A total of 265 patients (245 females; 20 males; mean age: 50.4±12.4; range, 19 to 79 years) diagnosed with primary SS, who presented to the Necmettin Erbakan University Faculty of Medicine Department of Internal Diseases Division of Rheumatology between March 1, 2011, and December 1, 2021, were included in the retrospective cohort study. Minor salivary gland biopsy specimens from the patients were evaluated by two experienced pathologists. Patients with comorbidities such as rheumatoid arthritis, systemic lupus erythematosus, systemic vasculitis, systemic sclerosis, lymphoproliferative disorders, malignancies, liver diseases, end-stage renal disease, diabetic nephropathy, active infections, recent blood transfusion, and a history of anemia were excluded from the study.

A focus score is a numerical expression of the degree of lymphocytic infiltration within a specific region of interest. In our study, a lymphocytic focus containing at least 50 lymphocytes in 4 mm^2 of glandular tissue in the pathology sample examined under a microscope was considered one focus.

All patients underwent the Schirmer test and ANA test, and those with a positive ANA result underwent ENA analysis. Minor salivary gland biopsies were performed on all patients. ANA was evaluated using the indirect immunofluorescence method, while the ENA profile was assessed using immunoblotting. The patients' Schirmer test results, ANA levels, ENA profile, including SSA, SSB, and Ro-52 values, and pathology data were recorded. The diagnosis of SS was made according to the 2016 American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) criteria. Patients diagnosed with SS before 2016 were reevaluated according to the 2016 ACR/EULAR diagnostic criteria, and those who did not meet the diagnostic criteria were not included in the study.

Statistical analysis

Data analysis was conducted utilizing IBM SPSS version 22.0 software (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to assess the normality of variables. All continuous data showed nonnormal distribution. Results were expressed as mean ± standard deviation for continuous variables and as numbers and percent for categorical variables. The chi-square test, independent sample t-test, and Mann-Whitney U test were used for the comparison of findings in two groups. Backward logistic regression analysis was used for regression analysis. A p-value <0.05 was considered statistically significant.

Table 1. Age, sex, and serological data of patients with primary Sjögren's syndrome

Variables	n	%	Mean±SD
Age (year)			50.4±12.4
Sex			
Female	245	92,5	
Focus score			
<1	43	16.2	
=1	105	39.6	
>1	117	44.2	
ANA			
Negative	62	23.4	
>1/160	104	39.2	
≥1/320	55	20.8	
≥1/640	42	15.8	
≥1/1280	2	0.8	
ENA			
Negative	152	57.4	
Positive	113	42.6	
Subtype of ENA			
SS-A	82	30.9	
SS-B	38	14.3	
Ro-52	79	29.8	

SD: Standard deviation; ANA: Antinuclear antibody; ENA: Extractable nuclear antibody.

RESULTS

A total of 265 patients with a confirmed diagnosis of SS were enrolled in the study. Patients' laboratory results, pathology findings, medication usage, and patterns of involvement were recorded by scanning the hospital system. The age, sex, and serological characteristics of the patients diagnosed with SS are provided in Table 1. The mean follow-up duration for patients diagnosed with SS was 63.1±31.9 months.

Extraglandular involvements in patients with SS were assessed, revealing that 32.5% of them exhibited such manifestations. These included joint involvement, lung involvement, central nervous system involvement, hematological involvement, hepatitis, and lymphoma. Table 2 presents information on extraglandular involvement and focus scores. It was noted that individuals with only glandular involvement predominantly utilized hydroxychloroquine, whereas those with extraglandular involvements required multiple medications, such as methotrexate, azathioprine, mycophenolate, cyclophosphamide, and rituximab, in addition to hydroxychloroquine. The mean duration from the diagnosis of SS to the occurrence of extraglandular involvement in patients was 15.2±27.8 months.

A comparison was conducted between patients who developed extraglandular involvement and those who had only glandular involvement in terms of ANA positivity, ANA titers, and ENA positivity. Among the ENA values, SSA, SSB, and Ro-52 were examined, and if one or more of these were positive, the patient was considered ENA positive. Within

Table 2. The distribution of attachment types and focus score

		Focus score							
		<1		=1		>1		Total	
	%	n	%	n	%	n	%	n	%
Extraglandular involvement negative	67.5	38	21.2	74	41.3	677	37.4	179	100
Extraglandular involvement positive	32.5								
Arthritis	73.26	2	3.2	25	39.7	36	57.1	63	100
Interstitial lung disease	9.30	-	-	3	37.5	5	62.5	8	100
CNS Involvement	6.98	1	16.7	1	16.7	4	66.7	6	100
Autoimmune hepatitis	3.49	1	33.3	-	-	2	66.7	3	100
Lymphopenia	2.33	-	-	1	50	1	50	2	100
Thrombocytopenia	2.33	-	-	1	50	1	50	2	100
Tubulointerstitial nephritis	1.16	1	100	-	-	-	-	1	100
Lymphoma	1.16	-	-	-	-	1	100	1	100

CNS: Central nervous system.

Table 3. Differences between patients with and without extraglandular involvement

	Extraglandular involvement						
	Positive			Negative			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Age (year)			52.7±11.5			49.3±12.8	0.041**
Focus score							0.001*
<1	5	5.8		38	21.2		
=1	31	36.0		74	41.3		
>1	50	58.1		67	37.4		
Duration of Illness (month)			62.5±31.4			63.4±32.1	0.885***
ANA							0.759****
Positive	67	77.9		136	76.0		
Negative	19	22.1		43	24.0		
ANA titer							0.668*
Negative	19	22.1		43	24.0		
>1/160	33	38.4		71	39.7		
≥1/320	17	19.8		38	21.2		
≥1/640	17	19.8		25	14.0		
≥1/1280	0	0		2	1.1		
ENA							0.283****
Positive	34	39.5		79	44.1		
Negative	52	60.5		100	55.9		
Subtype of ENA							
SS-A	25	29.1		57	31.8		0.648***
SS-B	16	18.6		22	12.3		0.171***
Ro-52	25	29.1		54	30.2		0.855***

SD: Standart deviation; ANA: Antinuclear antibody; ENA: Extractable nuclear antibody; * Pearson chi square test; ** Independent samples t test; *** Mann-Whitney U test; **** Fisher exact test.

Table 4. Regression analysis in patients with and without extraglandular involvement

			95% CI for Exp(B)	
	p	Exp(B)	Lower	Upper
Age	0.058	1.021	0.999	1.044
FS <1	0.002			
FS =1	0.032	3.071	1.100	8.574
FS >1	0.001	5.542	2.026	15.155
Constant	0.000	0.046		

Exp(B): Exponent value of B; FS: Focus score.

the scope of this investigation, it was observed that the focus score was significantly higher in patients who developed extraglandular involvement compared to those with only glandular involvement. Nevertheless, no significant differences were observed in terms of ANA positivity, ANA titers, and SSA, SSB, or Ro-52 positivity. The relevant statistical data are presented in Table 3.

In the backward logistic regression analysis conducted using the variables of focus score, age, sex, ANA positivity, ANA titers, and ENA positivity, it was found that age and focus score variables were associated with systemic involvement. For age, an odds ratio (OR) of 1.02 (95% confidence interval [CI]: 0.99-1.04) was obtained (p=0.058). In patients with a focus score of 1, the odds of involvement compared to focus

scores <1 were 3.07 times higher with an OR of 3.07 (95% CI: 1.10-8.57). In patients with focus scores >1, the odds of involvement compared to focus scores <1 were 5.54 times higher with an OR of 5.54 (95% CI: 2.03-15.15). The regression analysis presented in Table 4 demonstrates that there was no statistically significant difference in the other variables between patients with and without extraglandular involvement.

DISCUSSION

Within the scope of our study, it was observed that patients with SS who exhibited both glandular and extraglandular involvement had statistically significantly higher focus scores and were of advanced age compared to those with only glandular involvement. However, ANA positivity, ANA titers, and extranuclear antigen positivity were not found to be significant. In our study, it was found that in patients with primary SS who have both glandular and extraglandular involvement, the focus score and advanced age were statistically significant compared to patients with only glandular involvement. However, ANA positivity, ANA titers, and extranuclear ENA positivity (SSA, SSB, and Ro-52) were not deemed significant in the study.

The literature review revealed several studies on SS and extraglandular involvement. In a study focused on the focus score, patients were compared based on focus scores <1 and ≥1, and it was found that a higher focus score (≥1) was strongly associated with the phenotypic ocular and serological components of SS.[7] Kakugawa et al.[8] demonstrated in their study that a high focus score was associated with lung involvement. Another study found an association between focus scores and the development of lymphoma.[9] Retamozo et al.[10] classified the focus score as "unclear" regarding the development of lymphoma in their review. In our study, we observed a significantly higher focus score in SS patients with extraglandular involvement. Additionally, it has been demonstrated that as the focus score increases, the likelihood of extraglandular involvement also increases.

In a study focused on exocrine gland function in SS patients, it was found that SSA positivity and complement deficiency were associated with gland function.[11] Another study found that patients who were ANA positive, rheumatoid factor (RF) positive, and serologically positive were younger and predominantly female compared to negative patients, but no significant differences were observed in terms of clinical presentation of the disease.[12] García-Carrasco et al.[13] reported that lung involvement was more common in ANA-positive but ENA-negative patients. Ramos-Casals et al.[14] observed lymphadenopathy, elevated serum monoclonal immunoglobin levels, high RF, and SSA positivity in patients under the age of 35. Another study revealed higher glandular involvement, increased steroid requirement, and more frequent extraglandular leukopenia in patients positive for both ANA and anti-ENA.[15] Furthermore, the presence of anti-SSA/SSB has been associated with early disease onset, longer disease duration, parotid enlargement, hypergammaglobulinemia, elevated RF, and cryoglobulinemia.[16] In our study, no statistically significant differences were found in terms of ANA positivity, ANA titers, or ENA positivity between patients with extraglandular involvement and those with glandular involvement only.

In our study, we evaluated patients who had glandular involvement only as well as those who had both glandular and extraglandular involvement. No relationship was observed between ANA positivity or titers and SSA, SSB, or Ro-52 positivity with extraglandular involvement. While some studies have shown an association between SSA and glandular involvement, we did not find a significant relationship with extraglandular involvement in our study. It is possible that our study, being a clinical study, did not find significant findings due to the fact that serological positivity may not always manifest clinically or may have a delayed manifestation.

In our study, we found that patients with both glandular and extraglandular involvement in SS had significantly higher focus scores compared to those with glandular involvement only. In the literature review, the association between SS and focus scores has been studied as a prognostic factor in life-threatening conditions, such as interstitial lung disease and lymphoma, demonstrating a relationship between them.[8,9] Previous studies have investigated the relationship between focus scores and ocular

and serological markers,[11-16] but there is a lack of studies specifically focusing on extraglandular involvement that manifests clinically. The present study is valuable as it encompasses all clinically significant extraglandular involvements in SS patients. Alessandri et al.[17] demonstrated the dysregulation of autophagy in both salivary glands and peripheral T lymphocytes of SS patients, providing initial evidence of autophagy dysregulation in the pathophysiology of SS. The same study showed a positive correlation between salivary gland autophagy levels and $CD4^+$ T lymphocyte infiltration, as well as tissue expression of proinflammatory cytokines interleukin (IL)-21 and IL-23, along with a positive correlation between peripheral blood T lymphocyte autophagy levels and SS disease activity indices. These findings support the relationship between salivary gland involvement and systemic manifestations, as observed in our study. Another study by Bombardieri et al.[18] on the pathophysiology of primary SS and lymphoma demonstrated that ectopic lymphoid structures in salivary glands in primary SS sustain local antibody production and contribute to lymphomagenesis. These findings further support our study, suggesting a potential association between salivary gland inflammation and extraglandular involvement. SS is a disease that starts with glandular involvement and can manifest with various extraglandular involvements, leading to distinct clinical presentations. In patients with isolated glandular involvement, symptomatic treatment is usually sufficient, and no significant morbidity is observed. However, extraglandular involvements such as arthritis, central nervous system involvement, hematological manifestations, and lung involvement contribute to increased morbidity and healthcare requirements. Therefore, predicting extraglandular involvement in the disease is crucial for follow-up duration and immunosuppressive treatment decisions. The present study demonstrated that there is an increased pathological involvement of salivary glands in patients with extraglandular manifestations, and partially, advanced age is associated with a higher incidence of extraglandular involvement. Therefore, clinicians should not overlook the possibility of extraglandular involvement in patients with a focus score ≥1 in minor salivary gland biopsies and in advanced-age patients. Regular patient follow-up should be conducted, and if necessary, the appropriateness of immunosuppressive treatment should be reconsidered, with a specific focus on informing patients about the possibility of extraglandular involvement. Additionally, it is important to consider that as the focus score increases, the likelihood of extraglandular involvement also increases. Further advanced studies are still needed to elucidate the pathophysiology of SS and extraglandular manifestations.

A limitation of this study was its sample size of 265 patients. The strengths of our study lie in the comprehensive data available for all patients, encompassing serological markers, pathological results, medication usage, and clinical records. Through our investigation, it was observed that the assessment of focus scores could serve as a predictive indicator for extraglandular involvement in the disease. Therefore, performing biopsies on patients with SS may contribute significantly to clinicians by providing insights into potential future comorbidities.

In conclusion, focus scores were found to be higher in patients with extraglandular involvement. It was observed that as the focus score increased, the likelihood of extraglandular involvement also increased, and these patients were found to be older. While there was no significant difference between the two groups in terms of ANA positivity, ANA titers, and ENA positivity (SSA, SSB, or Ro-52), it was observed that focus score assessment could be a predictive indicator of extraglandular involvement in the disease. From a clinician's perspective, considering the disease classification criteria, a diagnosis can be made based on laboratory and objective evaluation of salivary gland and ocular dryness without performing salivary gland biopsy. However, in our study, since focus scores were determined to be a predictive value for extraglandular involvement in the disease, we emphasize the necessity of a biopsy.

Ethics Committee Approval: The study protocol was approved by the Necmettin Erbakan University Faculty of Medicine Ethics Committee (date: 07.04.2023, no: 173). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Idea/concept: M.Ç.E, P.O, R.T; Design: M.Ç.E, P.O, R.T; Control/supervision: P.O, R.T; Data collection and/or processing, writing the article: M.Ç.E, H.B, O.Y, F.K; Analysis and/or interpretation: M.Ç.E, O.Y, P.O, F.K; literature review: M.Ç.E, P.O; Critical review: P.O, R.T.

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