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Clinical and serological characteristics of anti-Ro/SS-A and anti-La/SS-B negative primary Sjögren's syndrome: a comparative study

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Abstract. – OBJECTIVE: This study aimed to describe the clinical spectrum of primary Sjögren's syndrome (pSS) patients with anti-Ro/SS-A and anti-La/SS-B negativity.

PATIENTS AND METHODS: From a single-center study population of consecutive SS patients fulfilling the 2016 ACR-EULAR classification criteria, those with triple seronegativity anti-Ro/SS-A (anti–Sjögren's-syndrome-related antigen A autoantibody), anti-La/SS-B (anti–Sjögren's-syndrome-related antigen B autoantibody), rheumatoid factor (RF) (-) and antinuclear antibody (ANA)(+)] or [anti-Ro/SS-A(-), anti-La/ SS-B(-), RF(+) and ANA(-)] and quad¬ruple seronegativity [anti-Ro/SS-A(-), anti-La/SS-B(-), RF(-) and ANA(-)] were identified retrospectively. Clinical, serological, and laboratory features were compared. A comparison between triple and quadruple seronegative pSS patients was also performed.

RESULTS: We included 184 patients (168 women, 16 men) with a mean age at diagnosis of 50.1±13.1 years. The most common subjective presenting features at the time of the diagnosis were dry mouth (94.5%) and dry eye (91.3 %). ANA positivity was 57.0%, and RF positivity was 30.4%. Salivary gland enlargement, arthritis, Raynaud's phenomenon, vasculitis, interstitial lung disease (ILD), neurological involvement, primary biliary cholangitis (PBC), lymphopenia, and thrombocytopenia were observed in ANA+ and RF+ patients but not in seronegative patients (p<0.0001). Arthritis was observed most frequently in RF-positive patients and secondly in ANA-positive patients, whereas arthritis was not observed in seronegative patients (p<0.0001). Autoimmune thyroiditis was present in 65 patients (35.0%), 84.6% of these patients were ANA positive while 12.3% were ANA negative (p=0.0014), RF positivity was 30.7% while RF negativity was 6.15% (p=0.001), 23.0% were both ANA and RF positive while 12.3% were seronegative (p<0.002). Cryoglobulinemia, renal disease, and lymphoma were not observed in any of the patients.

CONCLUSIONS: We confirm the strong influence of immunological markers on the phenotype of primary SS at diagnosis.

Key Words:

Primary Sjögren's syndrome, Auto-antibodies, Seronegativity, Antinuclear antibody (ANA), Rheumatoid factor (RF).

Introduction

Primary Sjögren's syndrome (pSS) is a systemic autoimmune disorder with a female predominance (9:1) and a peak incidence at approximately 50 years of age[1]. It is commonly characterized by xerophthalmia and xerostomia, although other systemic and organ-specific manifestations may occur[1]. The main factor in pathogenesis is that lymphocytes target exocrine glands[2]. SS is accompanied by a plethora of autoantibodies as a result of B cell aberrant activation, with anti-Ro/SS-A, anti-La/SS-B, rheumatoid factor (RF), and antinuclear antibody (ANA) being the most frequently encountered[3,4]. Anti-Ro/SS-A antibody is present in 50-75% of SS patients, and in approximately half of them, anti-La/SS-B antibody is also detected[5]. In previous studies[6], the prevalence of ANA and RF was 50-89% and 38-61%, respectively, in the sera of pSS patients. Immunological markers provide prognostic information both in the diagnosis of the disease and in predicting the results[7]. Some reports[8] indicated that RF may be associated with serological positivity for anti-Ro and anti-La, as well as with systemic severe disease, pulmonary involvement, renal disease, and corticosteroid use. In a different study[9], seronegative SS was found to be associated with less hematological malignancy.

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The relationship between autoantibody positivity and clinical findings in Sjögren's disease patients has been investigated more; however, the concept of seronegative has been forgotten. There are few studies in the literature, especially between RF and ANA antibodies and clinical entities.

The aim of this study is to explore the clinical landscape of SS patients with anti-Ro and anti-La negative autoantibody and investigate the effect of ANA and RF on the clinical expression of the disease.

Patients and Methods

The research cohort comprised 184 consecutive patients diagnosed with primary Sjögren's syndrome (pSS) who met the criteria established by the 2016 EULAR/ACR criteria[10]. These patients were retrospectively reviewed and followed from December 2019 to September 2023. Patients diagnosed with pSS with negative anti-Ro/SS-A and anti-La/SS-B antibodies and a focal score ≥1 on minor salivary gland biopsy (MSGB) were included in the study. Patients with a definite diagnosis of primary Sjogren's syndrome by MSGB were included in the study. The anti-double stranded DNA (anti-dsDNA), extractable nucleic antigen (ENA), and anti-cyclic citrullinated peptide (anti-CCP) antibodies were negative in all patients. In all patients, diseases that may cause secondary Sjögren were excluded by serologic tests and clinical findings. Systemic lupus erythematosus, rheumatoid arthritis, scleroderma, myopathies, mixed connective tissue disease, and fibromyalgia were excluded in all patients. It was defined as seronegative pSS (i.e., a lack of four autoantibodies in the serum). Clinical manifestations, laboratory data, and pathologic reports of patients were found in medical files and the computerized registry of the hospital. Patients without sufficient data for diagnosis of SS in the registry were not included in the study. Procedures general data and laboratory and clinical information at the onset of patients with pSS were retrospectively reviewed, including the first presentation and systemic involvements. Clinical data, such as age at diagnosis, disease duration, oral and ocular dryness, and constitutional symptoms, as well as data on joint, pulmonary, kidney, vasculitis, skin, nervous, gastrointestinal tract, and endocrine involvement, were collected. The levels of complements (C3 and C4), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), immunoglobulins (IgG, IgM, and IgA), ANA, RF, anti-Ro/SS-A, and anti-La/SS-B were retrieved from the case records. Schirmer's test was considered positive when less than 5 mm of the paper was humid after 5 minutes. An MSGB was taken from the lower lip by making an incision. Focal lymphocytic sialadenitis in an MSGB with one or more foci of lymphocytes per 4 mm^2 (focus score ≥1) was accepted as the histopathological criteria[11]. Direct immunofluorescence was used for the analysis of ANA. In antibody titer tests, the cutoff value for ANA was 1:100, in accordance with the values used in our laboratory. RF>20 IU/ml was considered positive. Patients with cytopenia were hematologically evaluated, and malignancy, leukemia, B12, and folate deficiency were excluded. ANA and RF positive and negative patients were compared according to clinical and laboratory findings. The study was approved by the Research Ethics Committee of the Eskişehir City Hospital (Ethics Committee No. ESH/GOEK 2023/31; date. 09/06/2023). The study was conducted according to good clinical practices and the Helsinki Declaration. Patients were invited for examination every 3 or 6 months, written informed consent was obtained from all participants at the time of application, and information was given about the study.

Statistical Analysis

While descriptive values were expressed as numbers (n) and percentages (%) for categorical values, they were expressed as the mean (standard deviation, SD) if normally distributed and as the median (interquartile range, IQR) if not normally distributed. Nonparametric analysis was performed using the Mann-Whitney U test. Student's *t*-test was used as a parametric test.

Differences in categorical data were analyzed by the Chi-square test. The statistical significance level was accepted as $p<0.05$ in all comparisons. All Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) 23.0 software (IBM Corp., Armonk, NY, USA).

Results

The baseline characteristics of the patients diagnosed with pSS are shown in Table I. The included patients were predominantly females (91.3%) with a mean age at diagnosis of 50.1±13.1 years. The most common subjective presenting features at the time of the diagnosis were dry mouth (94.5%) and dry eye (91.3 %). Arthralgia was the most

Table I. Baseline characteristics of 184 patients with primary Sjögren's syndrome.

Feature/ Clinical manifestation	Patients (%)
Age (mean ± SD)	56.3 ± 15.3
Age of diagnosis (mean ± SD)	50.1 ± 13.1
Gender (Female)	168 (91.3%)
Dry mouth	174 (94.5%)
Dry eyes	168 (91.3%)
Schirmer	
≤ 5 mm	125 (67.9%)
5-10 mm	53 (28.8%)
≥ 10 mm	6 (3.3%)
Focus score ≥ 1	184 (100%)
Salivary gland enlargement	22 (11.9%)
Arthralgias	108 (58.6%)
Arthritis	32 (17.3%)
Raynaud's phenomenon	9 (4.8%)
Anti-nuclear antibody (+)	105 (57.0%)
Rheumatoid factor (+)	56 (30.4%)
ESR (mm/h)	42.2 ± 28.7
CRP (mg/l)	10 ± 5.0
Leukopenia	28 (15.2%)
Anemia	44 (23.9%)
Lymphopenia	25 (13.5%)
Thrombocytopenia	6 (3.2%)
Hypergammaglobulinemia	36 (19.5%)
Hypocomplementemia	24 (13.0%)
Cryoglobulinemia	0
Vasculitis-purpura	3 (1.6%)
Interstitial lung disease	18 (9.7%)
Neurological involvement	
Central nervous system involvement	3 (1.6%)
Peripheral nervous involvement	2 (1.0%)
Autoimmune thyroiditis	65 (35.%)
Primary biliary cholangitis	8 (4.3%)
Renal disease	0
Malignancy	6 (3.2%)
Treatments	
Corticosteroids	50 (27.1%)
Hydroxychloroquine	175 (95.1%)
Methotrexate	15 (8.1%)
Azathioprine	12 (6.5%)
Cyclophosphamide	2 (1.0%)
Pilocarpine	22 (11.9%)

Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP).

common clinical finding except for dry mouth and dry eyes (58.6%). MSGB was found positive in all patients. ANA positivity was 57.0%, with the granular staining pattern at 65%, nuclear staining at 25%, homogenous staining at 5%, and centromere staining at 5%. ANA positivity was seen in 105 (57.0%) of the patients, while RF positivity was seen in 56 (30.4%). Both ANA and RF positivity were seen in 36 (19.6%) patients. The age at diagnosis of ANA-positive patients was younger than that of ANA-negative patients (45.1±10.2 *vs.* 49.3±12.1, p=0.023) (Table II). In the same situation, the age at diagnosis of RF-positive patients was earlier than that of RF-negative patients (50.3±10.1 *vs.* 56.2±12.3, p=0.032) (Table III). Patients with both ANA and RF positivity had a lower age at diagnosis compared to negative patients (46.1±12.2 *vs.* 53.3±9.1, p=0.003) (Table IV). Salivary gland enlargement was observed only in ANA and RF-positive patients but not in seronegative patients (p<0.0001). Arthralgias was seen only in RF-positive patients and patients with RF and ANA positivity together, while it was seen in 74.0% of isolated ANA-positive patients and never in seronegative patients (Table II). Arthritis and Raynaud's phenomenon were observed in ANA+ and RF+, but not in seronegative patients (p<0.0001) (Table IV). In addition, arthritis was seen most frequently in RF-positive patients and secondly in ANA-positive patients, whereas arthritis was not seen in seronegative patients. Patients who were ANA-positive had the highest mean ESR, while those who were RF-positive had the highest mean CRP. Leukopenia, anemia, lymphopenia, and thrombocytopenia were most frequently seen in ANA-positive patients, secondly in RF-positive patients, while lymphopenia and thrombocytopenia were never seen in ANA- and RF-negative patients. Cryoglobulinemia, renal disease, and lymphoma were not observed in any of the patients. Hypergammaglobulinemia was present in 19.5% of patients and was most common in ANA-positive patients, with a rate of 77.7%. Hypocomplementemia was most common in ANA positivity, second most common in RF positives, and less common in seronegative, respectively (p=0.260, p=0.002). Small vessel vasculitis was seen in 3 patients, and ANA was positive in all three patients. The number of patients with ILD at first presentation was 8.

While 15 (83.3%) of these patients had ANA positivity, 5 (27.7%) had RF positivity, and 3 (16.6%) had both ANA and RF positivity. There was no ILD involvement in seronegative. Neurological involvement was present in 5 patients (2.7%). ANA was positive in all of these patients, and ANA and RF were positive together in two of them. Autoimmune thyroiditis was present in 65 patients (35.0%), 84.6% of these patients were ANA positive while 12.3% were ANA negative (p=0.0014), RF positivity was 30.7% while RF negativity was 6.15% (p=0.001), 23.0% were both ANA and RF positive while 12.3% were seronegative (p<0.002). Of the autoimmune thyroiditis patients, 59 (90.7%) had Hashimoto's disease, 4 had Graves' disease, and 2 had subacute thyroiditis. PBC was present in

Table II. Clinical findings of patients according to ANA test.

Feature/Clinical manifestation	ANA positive n: 105, %	ANA negative n: 79	*p*-value
Age (mean ± SD)	53.9 ± 12.4	58.3 ± 13.0	0.029
Age of diagnosis (mean ± SD)	45.1 ± 10.2	49.3 ± 12.1	0.023
Female	102 (97.1%)	66 (83.5%)	0.014
Dry mouth	105 (100%)	69 (87.3%)	0.029
Dry eyes	100 (95.2%)	68 (86.2%)	0.121
Salivary gland enlargement	18 (17.1%)	0	< 0.0001
Arthralgias	80 (74.0%)	8 (10.1%)	0.004
Arthritis	10 (9.5%)	0	< 0.0001
Raynaud's phenomenon	7 (6.6%)	0	< 0.0001
ESR (mm/h)	49.7 ± 16.8	32.2 ± 18.7	0.0032
CRP (mg/dl)	9.4 ± 3.6	10 ± 8.0	0.860
Leukopenia	20 (19.0%)	2 (2.5%)	0.003
Anemia	30 (28.5%)	6 (7.5%)	0.025
Lymphopenia	22 (20.9%)	0	< 0.0001
Thrombocytopenia	5 (4.7%)	0	< 0.0001
Hypergammaglobulinemia	28 (26.6%)	2 (2.5%)	0.013
Hypocomplementemia	10 (9.5%)	4 (5.0%)	0.260
Vasculitis	3 (2.8%)	0	< 0.0001
Interstitial lung disease	15 (14.2%)	3 (3.7%)	0.045
Central nervous system involvement	3 (2.8%)	0	< 0.0001
Peripheral nervous involvement	2 (1.9%)	0	< 0.0001
Autoimmune thyroiditis	55 (52.3%)	8 (10.1%)	0.0014
Primary biliary cholangitis	8 (7.6%)	0	< 0.0001
Malignancy	3 (2.8%)	1 (1.2%)	0.480

Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antinuclear antibody (ANA).

Table III. Clinical findings of patients according to RF test.

Feature/Clinical manifestation	RF positive n: 56	RF negative n: 128	*p*-value
Age (mean ± SD) (year)	48.9 ± 9.4	53.0 ± 14.6	0.023
Age of diagnosis (mean ± SD) (year)	50.3 ± 10.1	56.2 ± 12.3	0.032
Female	53 (94.6%)	115 (89.8%)	0.460
Dry mouth	56 (100%)	118 (92.1%)	0.320
Dry eyes	49 (87.5%)	119 (92.9%)	0.730
Salivary gland enlargement	4 (7.1%)	0	< 0.0001
Arthralgias	56 (100%)	52 (40.6%)	0.016
Arthritis	28 (50%)	0	< 0.0001
Raynaud's phenomenon	2 (3.5%)	0	< 0.0001
ESR (mm/h)	41.2 ± 8.9	42.6 ± 10.3	0.970
CRP (mg/dl)	15.7 ± 8.5	7.5 ± 5.8	0.025
Leukopenia	5 (8.9%)	3 (2.3%)	0.032
Anemia	10 (17.8%)	4 (3.1%)	0.004
Lymphopenia	7 (12.5%)	0	< 0.0001
Thrombocytopenia	2 (3.5%)	0	< 0.0001
Hypergammaglobulinemia	10 (17.8%)	2 (1.5%)	0.003
Hypocomplementemia	8 (14.2%)	4 (3.1%)	0.002
Vasculitis	0	0	null
Interstitial lung disease	5 (8.9%)	0	< 0.0001
Central nervous system involvement	2 (3.5%)	0	< 0.0001
Peripheral nervous involvement	0	0	null
Autoimmune thyroiditis	20 (35.7%)	4 (3.1%)	0.001
Primary biliary cholangitis	2 (3.5%)	0	< 0.0001
Malignancy	2 (3.5%)	1 (0.7%)	0.046

Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF).

Table IV. Clinical findings of patients according to ANA and RF positivity and ANA and RF negativity.

Feature/Clinical manifestation	ANA and RF positive n: 36, %	ANA and RF negative n: 59	*p*-value
Age (mean ± SD)	50.9 ± 8.4	55.3 ± 11.0	0.046
Age of diagnosis (mean ± SD)	46.1 ± 12.2	53.3 ± 9.1	0.003
Female	34 (94.4%)	49(83.0%)	0.014
Dry mouth	36 (100%)	56 (94.9%)	0.049
Dry eyes	34 (94.4%)	52 (88.1%)	0.041
Salivary gland enlargement	4 (11.1%)	0	< 0.0001
Arthralgias	36 (100%)	30 (50.8%)	0.001
Arthritis	25 (69.4%)	0	< 0.0001
Raynaud's phenomenon	2 (5.5%)	0	< 0.0001
ESR (mm/h)	46.8 ± 14.8	36.2 ± 16.8	0.003
CRP (mg/dl)	8.4 ± 4.6	5.6 ± 4.6	0.039
Leukopenia	5 (13.8%)	6 (10.1%)	0.652
Anemia	10 (69.4%)	4 (6.7%)	0.002
Lymphopenia	7 (61.1%)	0	< 0.0001
Thrombocytopenia	2 (13.8%)	0	< 0.0001
Hypergammaglobulinemia	10 (69.4%)	4 (6.7%)	0.011
Hypocomplementemia	8 (22.2%)	4 (6.7%)	0.260
Vasculitis	0	0	null
Interstitial lung disease	3 (8.3%)	0	<0.0001
Central nervous system involvement	2 (5.5%)	0	< 0.0001
Peripheral nervous involvement	0	0	null
Autoimmune thyroiditis	15 (41.6%)	8 (10.1%)	0.002
Primary biliary cholangitis	2 (5.5%)	0	< 0.0001
Malignancy	2 (5.5%)	1 (1.2%)	0.480

Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), rheumatoid factor (RF), antinuclear antibody (ANA).

8 patients and all of these patients had ANA positivity, 2 of them had both ANA and RF positivity, and 7 patients were anti-mitochondrial antibody (AMA) positive. Hashimoto's thyroiditis was also present in 5 of 8 patients with primary biliary cholangitis (PBC). PBC patients were additionally treated with ursodeoxycholic acid (UDCA). Six patients had malignancy, including 3 patients with breast cancer, 1 with thyroid follicular cancer, 1 with colon cancer, and 1 with ovarian cancer. Hydroxychloroquine could not be administered because of contraindications in 3 patients and side effects in 6 patients, but it was administered to all patients except these. Immunosuppressive treatments were added according to organ involvement (Table I). The number of patients with a follow-up of more than three years was 56, and the number of patients with a follow-up of more than 1 year was 143. Lymphoma and death were not observed in these patients.

Discussion

Almost all autoimmune diseases (ADs) are related to circulating autoantibodies directed against self-proteins. Circulating autoantibodies can shed light on autoimmune pathways and clinical findings, and they play an important role in the diagnosis of autoimmune diseases, including pSS. In recent years, the number of classificatory autoantibodies for pSS has been reduced. For example, in 1993 European Criteria, 4 antibodies (ANA, RF, Ro/SS-A and/or La/SS-B) were established, in 2002 Criteria, only 2 (anti-Ro/SS-A and anti-La/SS-B), and in 2016 ACR/EULAR only one [(Ro/SS)-A] was included[10,12,13]. When the number of autoantibodies in the criteria was reduced, the concept of seronegative became more prominent. In this study, we examined the frequency and distribution of clinical phenotypes at the time of diagnosis according to serological tests. ANA positivity was 80% in a large cohort study, and we found ANA in 57% of patients with pSS, and as much the immunological marker most frequently detected[14]. We observed that patients with ANA positivity were referred to specialists dealing with autoimmune diseases earlier and were diagnosed earlier. ANA+ individuals exhibit a unique immunological landscape characterized by elevated levels of pro-inflammatory

mediators and antibody production, as well as upregulation of some type 1 interferon (IFN) genes, suggesting that even in the absence of autoimmune disease, a positive ANA might alter immune regulation and affect risk of other conditions[15]. The etiology of ADs includes genetic and environmental factors[16]. ADs are more likely to develop in genetically susceptible individuals, and three genes were found to be associated with SS[16]. Different genetic factors are interconnected with disease susceptibility, specific autoantibodies, and disease phenotypes[17]. Therefore, we observed organ involvement more frequently in ANA-positive patients than in negative patients. Salivary gland enlargement, arthralgias, arthritis, Raynaud's phenomenon, cytopenias, hypergammaglobulinemia, hypocomplementemia, vasculitis, ILD, neurological involvement, PBC, and autoimmune thyroiditis were more frequent in ANA+ patients than in ANA-negative patients (Table II). This finding is of clinical significance, highlighting the fact that among seronegative patients, those with positive ANA are expected to develop more severe disease manifestations as a consequence of a more generalized systemic autoimmune response. Previous studies[18] reported that the anti-Ro antibody was related to disease-specific symptoms and disease severity in pSS. Research[18] also suggested that anti-La antibodies, together with anti-Ro autoantibodies, may be associated with systemic activity in pSS. In parallel with these studies, we observed that extra glandular and organ involvement was higher in ANA-positive patients in our study. In Ro/SS-A and/or La/SS-B negative patients, ANA positivity, is an important predictive test for the organ-specific disease, and in ANA-positive patients, we recommend that thyroid, lung, liver, renal, skin, hematological, and neurological involvement should be investigated during diagnosis.

The frequencies of articular manifestations, cutaneous vasculitis, salivary gland enlargement, cytopenia, Raynaud's phenomenon, renal involvement, and central nerve system involvement were higher in RF-positive pSS patients than in RF-negative patients[19]. In our study, RF-positive was found at 30.4%, and all patients had arthralgia, arthritis was 50%, autoimmune thyroiditis at 35.7%, salivary gland enlargement at 7.1%, Raynaud's phenomenon at 3.5%, and cytopenia at 42.8%. In RF-negative patients, arthritis, salivary gland enlargement, Raynaud's phenomenon, cutaneous vasculitis, neurological involvement, and ILD were absent. Based on this, the most important risk factor for pSS-related arthritis is RF-positivity and the second most important risk factor is ANA positivity. Raynaud's phenomenon, a common sign of connective tissue disorders, is a vascular disorder characterized by reversible vasospasm of the digits induced by cold exposure[20]. It was shown[20] that Raynaud's phenomenon was seen in 13-38% of the patients with pSS. In the present study, we observed Raynaud's phenomenon in 4.8% of the patients with pSS, ANA, and RF positivity, which was found in 7 and 2 patients, respectively, and none in seronegative patients.

Previous multicenter studies[21] have found a significant relationship between low hypocomplementemia levels and extra glandular disease, immunological markers, and systemic findings. In our study, hypocomplementemia was seen in 24 patients (13.0%). Among these patients, complement levels were low in all 3 patients with cutaneous vasculitis, 8 patients with arthritis, 7 of 9 patients with Raynaud's phenomenon, 6 of 6 patients with thrombocytopenia, 6 patients with autoimmune thyroiditis, and 4 patients with ILD. Based on these results, low complement levels seem to be a risk factor for extra glandular involvement.

ILD reported in our cohort include cystic lung disease with lymphocytic interstitial pneumonitis (n=3), interstitial lung disease with NSIP pattern (n=13), and bronchiolitis obliterans with bronchiectasis (n=2). Treatments have included corticosteroids, azathioprine, mycophenolate mofetil, and cyclophosphamide.

Joint symptoms were associated with RF, and lymphopenia, thrombocytopenia, neurological involvement, and PBC were associated with ANA.

The overall rate of neurological involvement was 2.7% in our pSS cohort. The neurological involvement was peripheral neuropathy (2), and multiple sclerosis-like lesions in the central nervous system were the other involvement patterns (3).

In our study, autoimmune thyroiditis was the most common extra glandular involvement after arthritis and arthralgia, with a rate of 35.7%. ANA positivity was found in 55 (84.6%) and RF positivity in 20 (30.7%) patients. ANA staining pattern was granular at 45.4%, nuclear staining at 36.3%, and homogenous staining at 18.1%. Hashimoto's disease was the most common (90.7%), and 96.0% of the patients were receiving levothyroxine treatment. Our recommendation to

clinicians is to question the symptoms of Sicca in patients with Hashimoto's disease and to investigate those with symptoms in terms of Sjögren's disease.

PBC was present in 8 patients, and all patients had ANA positivity, and 2 patients had RF positivity. Hashimoto's disease was associated with 4 patients. All patients were given ursodeoxycholic acid. Cirrhosis did not develop in patients. PBC should be considered in persistent liver enzyme elevations in patients with Sjögren's disease.

A total of 19.5% of our patients had also high immunoglobulin levels. 77.7% of patients were ANA positive and 27.7% were RF positive. Salivary gland enlargement in 22.2% of patients with hypergammaglobulinemia, arthralgia in 69.4%, Raynaud's phenomenon in 11.1%, and immunoglobulin levels were high in 3 of 5 patients with neurological disorders. Although the number of patients with hyperimmunoglobulinemia was low, our findings also suggest that elevated serum immunoglobulin levels may have a significant predictive value in SS diagnosis. Larger studies are needed to reveal this assertion.

In this study, we observed differences in clinical findings according to RF and ANA positivity. Based on this, we suggest that organ involvement should be questioned and investigated according to autoantibody positivity in pSS patients.

Limitations

There are several limitations to this study. Firstly, the small sample size of the pSS cohort results in limited meaningful statistical analysis. The seronegative pSS group was relatively small. The study group comprised patients who attended a single center and the retrospective design of our study. The relationship between disease activity and systemic involvement could not be evaluated due to a retrospective study. Cryoglobulinemia was studied in only 16 patients and was negative in all patients. It was studied only in patients with RF positivity and complement deficiency and in patients with vasculitis and neurological involvement.

Conclusions

In some pSS cases, circulating autoantibodies were not present. The clinical features of these cases were different from those of ANA and RF-positive pSS. The age of diagnosis is earlier, especially in those with positive serological tests. Extra glandular organ involvement is more common in RF and ANA-positive patients compared to seronegative patients. Immunological patterns play a central role in the phenotypic expression of the disease at the time of diagnosis and may guide physicians in designing specific personalized management during the follow-up of patients with primary SS.

Conflict of Interest

The author declares no conflict of interest.

Ethics Approval

This study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Research Ethics Committee of the Eskişehir City Hospital (No. ESH/GOEK 2023/31; date 09/06/2023), and it was carried out according to the ethical standards stated in the Declaration of Helsinki and its amendments.

Informed Consent

Written informed consent was obtained from the study participants.

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Data Availability

Data information can be obtained from the author upon request.

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