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NEÜ YAYINEVİ

Hematological Involvement in Sjögren's Syndrome and The Relationship of Involvement with Salivary Gland Biopsy

Sjögren Sendromunda Hematolojik Tutulum ve Tutulumun Tükrük Bezi Biyopsisi ile İlişkisi

Mustafa Cagri Ergun[1], Okancan Yilmaz[2], Emine Buyukboz[3], Busra Gokce[3], Yusuf Cihat Turkmenoglu[3], Pembe Oltulu[2], Sidika Findik[2], Recep Tunc[1]

[1]Necmettin Erbakan University, Medical Faculty, Division of Rheumatology, Department of Internal Medicine, Konya, Turkey
[2]Necmettin Erbakan University, Medical Faculty, Department of Pathology, Konya, Turkey
[3]Necmettin Erbakan University, Medical Faculty, Department of Internal Medicine, Konya, Turkey

Address correspondence to:
Mustafa Cagri Ergun, Necmettin Erbakan University, Medical Faculty, Division of Rheumatology, Department of Internal Medicine, Konya, Turkey
e-mail: mustafacagriergun@gmail.com

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Öz

Amaç: Sjögren sendromu (SS), glandular bez iltihabı ile karakterize kronik, multisistemik otoimmün hastalıktır. SS hematolojik tutulum da dahil çok farklı ekstraglandüler tutulumlar yapabilmektedir. Çalışmamızın amacı SS hastalarında hematolojik ve patolojik veri olan Fokus skoru (FS) ve Mason Chisholm Skoru (MS) ile ilişkisini değerlendirilmektir.
Hastalar ve Yöntemler: Çalışmaya 101 SS olan hasta ve 91 kontrol grubu alınmıştır. Tüm SS hastalarına 2016ACR/EULAR kriterlerine göre yeni tanı konmuştur. Hemogram bozukluğuna neden olabilecek ek hastalıklara sahip hastalar çalışmadan dışlanmıştır.
Bulgular: Nötrofil, monosit ve platelet değerleri istatistiksel olarak anlamlı düşük çıkmış (p=0.000, p=0.002, p=0.016); lenfosit ve hemoglobin değerleri kontrol grubuna göre düşük olsa da istatistiksel olarak anlamlı çıkmamıştır (p=0.053, p=0.685). Korelasyon analizinde hem FS ve MS'unun nötrofil (r=-0.329, p<0.01), lenfosit (r=-0.264, p<0.01), monosit (r=-0.306, p<0.01) ve platelet (r=-0.220, p<0.01) ile negatif korele bulunmuştur.
Sonuç: SS hemogramda sitopeniler yapabilmektedir ve nötropeni, anemi ve trombositopeni, FS ve MS ile negatif korelasyon göstermektedir. Bu yüzden tanı anında yüksek FS ve MS olan hastalarda hematolojik tutulum açısından dikkatli olunmalı, hastalar SS kriterlerini karşılasa dahi minör tükrük bezi biyopsisi yapılmalıdır.

Anahtar Kelimeler: Sjögren sendromu, minör tükrük bezi biyopsisi, fokus skoru, sitopeni

Abstract

Aim: Sjögren's syndrome (SS) is a chronic, multisystem autoimmune disease characterized by inflammation of the glandular tissues. SS can manifest with various extraglandular involvements, including hematologic complications. The aim of our study is to evaluate the relationship between hematologic and pathological data, specifically focusing on the Focus Score (FS) and the Mason Chisholm Score (MS), in SS patients.
Patients and Methods: The study included 101 patients with Sjögren's syndrome (SS) and 91 individuals in the control group. All SS patients were newly diagnosed according to the 2016 ACR/EULAR criteria. Patients with comorbidities that could lead to hematological disorders were excluded from the study.
Results: The neutrophil, monocyte, and platelet values were found to be statistically significantly lower (p=0.000, p=0.002, p=0.016), while lymphocyte and hemoglobin values, although lower in the SS group compared to the control group, did not reach statistical significance (p=0.053, p=0.685). Correlation analysis revealed a negative correlation between both the FS and MS scores and neutrophil (r=-0.329, p<0.01), lymphocyte (r=-0.264, p<0.01), monocyte (r=-0.306, p<0.01), and platelet (r=-0.220, p<0.01) values.
Conclusion: SS can potentially induce cytopenias in the hemogram, with neutropenia, anemia, and thrombocytopenia displaying a negative correlation with FS and MS. Consequently, in patients with elevated FS and MS scores at the time of diagnosis, it is crucial to exercise caution regarding hematological involvement. Even if patients meet the SS diagnostic criteria, a minor salivary gland biopsy should be considered.

Keywords: Sjögren syndrome, minor salivary gland biopsy, focus score, cytopenia

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INTRODUCTION

Sjögren syndrome (SS) is a chronic, multisystem autoimmune disease characterized by inflammation of the tear and salivary glands, resulting in dryness of the eyes and mouth. It can also manifest with various extraglandular symptoms. This pathology, described by some authors as autoimmune epithelitis, can occur independently or coexist with other autoimmune diseases (1).

Between 60 to 80 percent of individuals affected by Sjögren's syndrome are characterized by the presence of autoantibodies, particularly anti-Ro/SSA and anti-La/SSB. Antinuclear antibodies (ANA) are found in approximately 90 percent of patients, and high titers of rheumatoid factor are also frequently observed. Autoantibodies can be positive years before the clinical onset of SS (2). The primary pathological lesion of Sjögren's syndrome is lymphocytic infiltration of the salivary and lacrimal glands. The infiltrates consist of focal clusters of lymphocytes that start around the ducts and extend to involve the entire lobule. The cellular composition of these infiltrations depends on the severity of the disease. Initially, T cells, especially CD4+ cells, dominate in milder infiltrates that conform to the gland's architecture. B cells become more prominent in larger and denser infiltrates associated with acinar destruction and loss of tissue structure (3).

Patients with SS have an increased risk of non-Hodgkin lymphoma compared to the general population. This association is well-established for various autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus, and celiac disease, but the highest risk is observed in SS patients (4). Persistent enlargement of the salivary glands is a significant clinical risk factor. Other risk factors include cutaneous vasculitis, lymphadenopathy, splenomegaly, cryoglobulinemia, and the development of glomerulonephritis (5). SS can also lead to anemia and leukopenia, especially in patients positive for SS-A and SS-B antibodies (6).

The purpose of our study is to examine the cellular types of hematological involvement in SS patients and evaluate the relationship between cellular involvement and pathological data using the Focus Score (FS) and Mason Chisholm Score (MS).

PATIENTS AND METHODS

Study population

The study included a total of 101 patients diagnosed with primary Sjögren's syndrome who visited the Rheumatology outpatient clinic at Necmettin Erbakan University Medical Faculty Hospital between 01.03.2021 and 01.12.2021. The study was approved by the medical ethics committee of the hospital (07.04.2023- 2023/4279/13662). A control group of 91 individuals who underwent salivary gland biopsy for various reasons was also included. All participants included in this study were newly diagnosed with SS and had not received any prior treatment for SS. Minor salivary gland biopsy samples were collected from the patients and evaluated by two experienced pathologists.

Patients with concomitant autoimmune diseases, lymphoproliferative diseases, malignancies, end-stage renal and liver disease, diabetic nephropathy, active infections, recent blood transfusions, and a previous history of anemia, were excluded from the study.

Demographic and clinical data

All patients underwent Schirmer's test and ANA test. In patients with positive ANA results, ENA (extractable nuclear antibody) analysis was performed. Minor salivary gland biopsy was performed on all patients. ANA was evaluated using the indirect immunofluorescence (IIF) method, and ENA profile was assessed using the Immun Blot (IB) method. The values of Schirmer's test, ANA, ENA profile (including SS-A, SS-B, RO-52), and pathological data were recorded for each patient. The diagnosis of Sjögren's syndrome was established according to the 2016 ACR/EULAR criteria.

Statistical analysis

Data analysis was conducted using SPSS version 22.0 (SPSS Inc., Chicago, IL, USA). A p-value of less than 0.05 was considered statistically significant. The normality of variables was assessed using the Kolmogorov-Smirnov test, and it was found that all continuous variables had a non-normal distribution. Continuous variables were presented as mean (standard deviation), while categorical variables were presented as numbers and percentages. The comparison of findings between the two groups was performed using the Chi-square test and Mann-Whitney U test. Correlations were analyzed using the two-tailed Spearman correlation analysis.

RESULTS

A total of 101 patients with primary Sjögren's syndrome and 91 individuals in the control group were included in the study. The demographic and serological information of patients diagnosed with

Table 1. Demographic Data in Primary Sjögren's Syndrome

Variables	Values
Age (year old)	51.1 (±12.9)
Female gender (N, (%))	95 (94.0%)
ANA (N)	
Negative	17 (16.9%)
Positive	84 (83.1%)
ENA (N)	
Negative	40 (39.6%)
SS-A	20 (19.8%)
SS-B	2 (1.9%)
RO-52	30 (29.7%)
Multiple Positive	9 (8.9%)
Schirmer Score	3.63 (±3.1)

Note: Values are expressed as mean (± SD), Number(N) and percentage(%)

SS is displayed in Table 1. No statistically significant variations in age and gender distribution were observed between the patient group and the control group. As anticipated, the Focus Score and Mason Chisholm scoring systems, which are acknowledged as pathological classifications for SS, demonstrated statistically significant differences in the patient group compared to the control group.

When examining the hemogram results of the patients, it was observed that there was a decrease in both the myeloid and lymphoid series cells. Among them, neutrophil, monocyte, and platelet values were found to be statistically significantly lower (p=0.000, p=0.002, p=0.016); although lymphocyte and hemoglobin values were lower in the patient group compared to the control group, they did not

Table 2. Comparison of pathology and hemogram results of patients with primary Sjögren's syndrome

Variables	SS	Control	P
Sex (Female) N(%)	95 (94.0%)	79 (86.8%)	0.135[1]
Age (years)	51.5(±12.9)	46.6(±13.1)	0.104[2]
Focus Score			<0,001[2]
<1	6 (5.9%)	91 (100%)	
=1	74 (73.2%)		
>1	21 (20.7%)		
Mason Chisholm Score	3.48 (±0.74)	1.37(±0.69)	<0.001
0	0 (0%)	17 (18.7%)	
1	4 (3.9%)	38 (41.8%)	
2	2(1.9%)	35 (38.5%)	
3	37 (36.6%)	1 (1.1%)	
4	58 (57.4%)	0 (0%)	
WBC	6.53(±2.3)	8.01(±2.6)	0.637[2]
NEU	3.82(±1.8)	4.86(±2.3)	0.000[2]
LYM	2.12(±0.8)	2.4(±0.8)	0.053[2]
MON	0.48 (±0.17)	0.54 (±0.15)	0.002[2]
HGB	13.1 (±1.2)	13.2 (±1.3)	0.685[2]
PLT	292(±326)	289(±83)	0.016[2]

[1] Fisher's Exact Test, [2] Mann–Whitney U test

Note: Results are provided as mean ± SD for continuous variables and number (percentage) of patients for categorical variables. Abbreviations: WBC, white blood cell; NEU, neutrophil; LYM, lymphocyte; MON monocytes; HGB, hemoglobin; PLT, platelet

Table 3. Correlation of Hemogram and Pathological Scoring Grades

		1	2	3	4	5	6	7
1	WBC	1						
2	NEU	0.912*	1					
3	LYM	0.608*	0.329*	1				
4	MON	0.534*	0.451*	0.369*	1			
5	HGB	-0.017	-0.053	0.102	-0.041	1		
6	PLT	0.422*	0.390*	0.296*	0.272*	-0.137	1	
7	Focus Score	-0.106	-0.301*	-0.240*	-0.229*	-0.056	-0.204*	1
8	Mason Score	-0.139	-0.329*	-0.264*	-0.306*	-0.113	-0.220*	0.887*

WBC, white blood cell; NEU, neutrophil; LYM, lymphocyte; MON monocytes; HGB, hemoglobin; PLT, platelet *p<0.01

reach statistical significance (p=0.053, p=0.685). The comparison of pathology and hemogram results in SS patients is presented in Table 2.

The correlation analysis between hemogram values and FS and MS is presented in Table 3. In the correlation analysis between FS and hemogram values, a negative correlation was found with neutrophil (r=-0.301, p<0.01), lymphocyte (r=-0.240, p<0.01), monocyte (r=-0.229, p<0.01), and platelet (r=-0.204, p<0.01) values. Similarly, in the MS score, a negative correlation was observed with neutrophil (r=-0.329, p<0.01), lymphocyte (r=-0.264, p<0.01), monocyte (r=-0.306, p<0.01), and platelet (r=-0.220, p<0.01) values. Additionally, as expected, a positive correlation was found between FS and MS (r=-0.887, p<0.01).

DISCUSSION

In our study, it was observed that both monocytes and lymphocyte series cells showed a decreasing trend in the hemogram results of the patients. Among them, neutrophil, monocyte, and platelet values were found to be statistically significantly lower, while lymphocyte and hemoglobin values were lower in the patient group compared to the control group, but did not reach statistical significance. In the correlation analysis, it was found that both FS and MS were negatively correlated with neutrophil, lymphocyte, monocyte, and platelet values.

Leukopenia has been reported in both case studies and large-scale epidemiological investigations (7-9). Furthermore, a few studies have suggested that it may be a risk factor for lymphoma (10-12). However, the clinical characteristics and underlying pathogenic mechanisms of leukopenia associated with SS have not been completely clarified. In our study, similar to the literature, we observed a decreased white blood cell count in SS patients compared to the control group, but it did not reach statistical significance.

There are no studies specifically focusing on SS and neutropenia in the literature. Most studies in this area are generally related to the etiopathogenesis of neutropenia in SLE. One study conducted on SLE patients with neutropenia showed a significant negative correlation between neutrophil count and serum Tumor Necrosis Factor-Related Apoptosis Inducing Ligand (TNFSF10/TRAIL) levels (13). TRAIL has been reported to be associated with the pathogenesis of some autoimmune diseases such as Sjögren's syndrome, autoimmune encephalomyelitis, and thyroid disease (14-16). The exact pathogenesis of neutropenia in SS is not fully understood. In our study, we also observed a statistically significant decrease in neutrophil levels in SS patients compared to the control group. The decrease in neutrophil levels showed a negative correlation with FS and MC in the minor salivary gland biopsy.

Autoimmune diseases are frequently complicated by immune thrombocytopenic purpura (ITP), although the precise mechanisms underlying platelet destruction remain uncertain (17). Elevated levels of plasma P-selectin autoantibodies have been proposed to potentially contribute to the pathogenesis of ITP in patients with SS (18). Chen et al. (19) highlighted a significant decrease in FcyRIIb expression on B cells in SS patients with severe thrombocytopenia. These studies suggest the involvement of humoral immune response in platelet destruction in SS. However, the specific autoantibodies that may contribute to platelet destruction and the involvement of T cells in ITP in SS have not been investigated yet. Consistent with the literature, our study also revealed statistically significant thrombocytopenia in SS patients compared to the control group. Furthermore, thrombocytopenia showed a negative correlation with the Focus score and Mason Chisholm score.

Mild normocytic normochromic anemia is frequently observed in patients with SS (20). Severe anemia is uncommon, and in the literature, only a few cases of severe autoimmune hemolytic anemia (AIHA) have been reported (21). Tishler et al. (22) noted that elderly-onset SS patients tend to have slightly milder clinical symptoms and fewer immunological markers compared to younger-onset SS patients. Studies have shown that AIHA in SS patients is associated with a higher prevalence of autoantibodies (ANA, SSA, etc.) compared to those without anemia, and the anemia tends to be more severe (23). Consistent with the literature, our study observed a decrease in hemoglobin levels in SS patients compared to the control group, although it was not statistically significant.

In a study investigating lymphocytes, it was observed that naïve CD4+ T cells in SS patients had a lower frequency of Ki67+ cell proliferation compared to the control group. Additionally, naive CD4+ T cells obtained from SS patients showed decreased proliferative response to in vitro IL-7 stimulation, suggesting impaired homeostatic T-cell proliferation in individuals with the disease (24). In our study, lymphocyte count in SS patients showed a decrease similar to the literature but was not statistically

significant compared to the control group. However, a negative correlation was observed between FS and MS scores based on the salivary gland biopsy results.

Numerous studies in the literature have demonstrated the association between monocytes and the pathogenesis of SS. TRAIL is a cytokine that plays a role in the regulation of immunity. Studies have shown that TRAIL plays a critical role in SLE, other rheumatic diseases, and lung damage (25-28). In a study, researchers demonstrated an elevated expression of TRAIL in monocytes of SS patients, suggesting that TRAIL-expressing monocytes may have a significant role in the pathogenesis of SS (29). Wildenberg et al. (30) also reported an increase in IFN-associated genes, such as IFI27, IFITM1, IFIT4, and IFI44, in monocytes of SS patients. Despite the studies mentioned concerning the association between monocytes and SS pathogenesis, no study related to monocyte depletion has been found. In our study, we observed a decreased level of monocytes in SS patients compared to the control group. Furthermore, the monocyte count showed a negative correlation with the focus score and MS score.

In our study, we observed a decrease in all hematological series, and statistically significant lower levels of neutrophils, monocytes, and platelets were found. The negative correlation between the levels of neutrophils, lymphocytes, monocytes, platelets, and the FS and MS was interpreted based on the results of minor salivary gland biopsy. Although there was a decrease in leukocyte and lymphocyte levels, the results did not reach statistical significance, which could be attributed to the early stage of the disease at the time of diagnosis. Our study found that hematological involvement increased with the histopathological grade of minor salivary gland involvement after biopsy. Upon reviewing existing studies, it was found that only lymphocyte and leukocyte levels were examined in relation to the severity of minor salivary gland involvement. Our study is novel in comparing all hematological cell series with FS and MS.

Neutropenia in patients with Sjögren's syndrome, especially when it drops below 500/μL, may be associated with an increased risk of infection. Autoimmune neutropenias are often undetected since symptoms are not pronounced, and reliable markers for neutrophil lysis are lacking. Bacterial infections, particularly recurrent stomatitis, periodontal inflammation, perirectal abscess, cellulitis, pneumonia, and septicemia, are more common. Considering the decreased exocrine secretions in SS patients, it can be anticipated that oral cavity, upper and lower respiratory tract infections would be frequent. Although anemia is common in SS patients, AIHA is rare but can lead to severe clinical outcomes. Anemia-related symptoms such as fatigue, weakness, and impaired quality of life may occur. Mild petechiae due to thrombocytopenia, especially in the context of middle-aged to older patient population and multiple medication use, may be associated with gastrointestinal bleeding. In our study, although the patients' initial hemogram results were taken at the time of diagnosis, cytopenias were present compared to the control group, and these cytopenias correlated with salivary gland involvement. Therefore, clinicians should be cautious in patients with high FS and MS, as hematological involvement may increase as the histopathological grade increases. The 2016 ACR/EULAR criteria are commonly used in the diagnosis of Sjögren's syndrome. In classification using scoring, patients can receive a diagnosis without undergoing minor salivary gland biopsy. However, considering that our study showed an increase in hematological involvement as FS and MS increased, it is important to assess hematological involvement despite meeting the diagnostic criteria.

The main limitation of the study is the lack of long-term follow-up of hematological parameters in patients. However, considering that the parameters can be influenced by the treatment administered after diagnosis, a long-term follow-up study was not conducted. The strength of our study is that it was conducted using laboratory values obtained before the initiation of immunosuppressive treatment, which could affect the hemogram results in patients.

CONCLUSION

SS can cause cytopenias in the hemogram, and there is a negative correlation between neutropenia, anemia, and trombositopenia with the FS and MS observed in the salivary gland biopsy. Therefore, in patients with high-grade involvement at the time of diagnosis, caution should be exercised regarding hematological involvement, and even if patients meet the classification criteria for diagnosis, a minor salivary gland biopsy should be performed.

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Address correspondence to: *Mustafa Cagri Ergun, Necmettin Erbakan University, Medical Faculty, Division of Rheumatology, Department of Internal Medicine, Konya, Turkey*
e-mail: *mustafacagriergun@gmail.com*

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