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Letter to Editor / Editöre Mektup

IS SERONEGATIVE SJÖGREN'S SYNDROME: AN OVERLOOKED ENTITY?

SERONEGATİF SJÖGREN SENDROMU: GÖZDEN KAÇAN BİR ANTİTE Mİ?

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Dear Editor,

Primary Sjögren's syndrome (PSS) is a systemic autoimmune disease. It causes chronic inflammation and dysfunction of the exocrine glands, especially the salivary glands, resulting in dryness of the eyes and mouth. An estimated 0.01% to 0.72% of the population is affected by Sjögren's syndrome (1). Patients may present with a range of clinical manifestations, from sicca symptoms to potentially severe extra glandular and/or systemic features. These may include inflammatory arthritis, parotitis, interstitial lung disease, neurological dysfunction, cryoglobulinaemia and lymphomas. SS diagnosis is based on the combination of clinical, serological, and functional tests with histological biomarkers. To diagnose PSS, internationally accepted classification criteria require objective measures of reduced tear or saliva production, as well as immunological abnormalities confirmed either by detecting anti-SSA/Ro autoantibodies or through histological findings of focal lymphocytic sialadenitis in labial salivary glands (2). Patients with SS commonly present with autoantibodies such as anti-Ro/SSA, anti-La/SSB, antinuclear antibodies (ANA), and rheumatoid factors (RF). Patients who meet the criteria for SS but do not have the typical serum antibodies are referred to as seronegative SS patients. The prevalence of seronegative SS in SS cohorts varies widely in the literature, ranging from 8% to 37% (3). Minor salivary gland biopsy (MSGB) represents the cornerstone for the diagnosis of seronegative pSS, allowing the study of the characteristic focal infiltration of B- and T lymphocytes. Here we present 3 cases of seronegative SS with different organ involvement (Table 1).

A 54-year-old woman was admitted to the pulmonology department 1 year ago with the complaint of increasing dyspnea, which had been present for about 2 years. In the Computed tomography (CT) taken; diffuse peribronchovascular thickening and ground glass changes with tiny cysts along the bronchovascular bundles in both lungs (lymphocytic interstitial pneumonia) have a pattern and in respiratory function tests (FEV1 63%, FVC 71%, and DLCO 70%), ıdiopathic interstitial lung disease was considered due to its restrictive character. She was treated with inhaled bronchodilators and systemic steroids when necessary. She has been referred to us for rheumatological diseases due to joint pain. On questioning, she stated that she had dry mouth for an average of 3-4 years, she did not know about dry eye. Schirmer test was <5 mm/5 minutes. ANA, RF, anti-Ro/SSA, and anti-La/SSB were negative. The erythrocyte sedimentation rate (ESR) was 25 mm/h, and C-reactive protein (CRP) was 1 mg/dl (0-5). On MSGB, the focus score was >1 and 4 lymphocytic aggregates and amyloid staining was negative. PSS was diagnosed and prednisolone and cyclophosphamide treatment was started. The patient whose dyspnea decreased with treatment, is in the 18th month of treatment and continues to be followed up with azathioprine 150 mg/day and prednisolone 5 mg/day.

A 48-year-old female patient was examined with fatigue and joint pain, in laboratory tests performed total bilirubin 2.57 mg/dL (0.3-1.2 mg/dL), gamma-glutamyl transpeptidase (GGT) 570 IU/L (normal < 55 IU/L) and Alkaline phosphatase 280 IU/L (normal 30-120 IU/L), aspartate transaminase (AST) 112 IU/L (normal 8-35 IU/L) and alanine transaminase (ALT) 125 IU/L (normal 10-45 IU/L) levels high. The immunological study confirmed the presence of positive anti-mitochondrial antibody (AMA) and negative ANA and anti-smooth muscle antibodies (ASMAs). A liver biopsy was performed after confidently ruled out viral, metabolic, and malignant causes. The liver biopsy revealed an expansion of port spaces due to an abundance of inflammatory infiltrate, primarily consisting of lymphocytes and plasma cells, with rare eosinophils. Additionally, there was evidence of interface hepatitis and peri-portal fibrosis. Primary biliary cholangitis(PBC) was considered in the patient. The patient was started on ursodeoxycholic acid and her cholestasis enzymes decreased during follow-up. She was referred to us due to rheumatological diseases due to pain in her fingers and wrist. It was learned that she had dry mouth for 4-5 years and dry eye for 2 years and that she used tears. On physical examination, she had arthralgia, and her tongue was dry. ANA, RF, anti-Ro/

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Table 1. Baseline characteristics of three patients with primary Sjögren's syndrome.

Feature/Clinical manifestation	Case 1	Case 2	Case 3
Age	54	48	44
Gender/female	+	+	+
Dry mouth	+	+	+
Dry eyes	+	+	+
Schirmer / mm/5 minute	<5	<5	<5
Focus score	>1	>1	>1
Anti-SSA/Ro and anti-La/SSB	negative	negative	negative
ANA and RF	negative	negative	negative
ESR (mm/h)(0-20)	25	32	40
CRP (mg/dl)(0-5)	1	3	25
Arthralgias	+	+	+
Arthritis	-	-	-
Parotitis	-	-	+
Interstitial lung disease	+	-	-
Primary biliary cholangitis	-	+	-
Treatments	Corticosteroids Hydroxychloroquine Cyclophosphamide	Corticosteroids Hydroxychloroquine	Corticosteroids Hydroxychloroquine Antibiotics

ANA: Antinuclear antibody, RF: Rheumatoid factor, ESR: Erythrocyte sedimentation rate, CRP:C-reactive protein

SSA, and anti-La/SSB were negative in serological tests and MSGB was performed. Focus score>1 and there were 3 aggregates. PBC overlap with PSS was considered. Hydroxychloroquine 200 mg/day and prednisolone 5 mg/day were added to treatment. She is in the 12th month of her treatment and her follow-up and treatment continue.

A 44-year-old woman was referred for evaluation of painful, bilateral parotitis. The patient had a history of recurrent parotitis episodes occurring every one or two months for the past four years. These episodes were associated with elevated levels of CRP and which usually required antibiotic therapy. On questioning, the patient had dry mouth, dysphagia and arthralgia. The dry eye was unknown. The patient's physical examination revealed mildly swollen parotid glands bilaterally. Laboratory tests showed ANA, RF, anti-Ro/SSA, and anti- La/SSB negative. Schirmer test <5 mm/5 minutes. A labial biopsy of MSGB showed six lymphoid aggregates, several focuses on periductal lymphoid cell infiltration with glandular and ductal atrophy. The patient has been diagnosed with PSS based on these findings. Hydroxychloroquine 200 mg/day and prednisolone 5 mg/day were initiated for PSS. She was started on a prophylactic course of amoxicillin–clavulanic acid 1000 mg twice a day (seven days), after a month this was reduced to 500 mg every evening. After six months of remission of parotitis attacks, prophylactic therapy was stopped. In the 9th month of her treatment, her follow-up continues without parotitis attacks.

Diagnosing PSS can indeed be challenging. Approximately 30% of cases involving dryness in mucous membranes are attributed to age-related glandular atrophy or medication use (4). Sicca symptoms are widely prevalent in the general population and can have a variety of causes, the large majority of which are not associated with autoimmune disease (5). As a result, pSS might be overlooked. Seronegative Sjögren's syndrome can be accurately diagnosed by identifying autoantibody biomarkers associated with SS through a MSGB. It is important to perform further investigations to avoid missing this diagnosis in clinical settings. Seronegative patients often face delayed diagnosis compared to their seropositive counterparts (6). In a study conducted in seronegative patients, it was observed that SSA/Ro-52 autoantibodies were detected in saliva before autoantibodies appeared in serum (7). It has been stated that this method may help in the early detection of autoimmunity and can replace serum anti-SSA/Ro Ab (7). Based on this, the concept of seronegativity may be expanded in the coming years to include not only plasma antibodies but also salivary glands antibody negativity. Moreover, we must persist in conducting further research to discover novel disease-specific autoantibodies, thereby making substantial advancements in the diagnosis of these patients. Serological classification of patients can aid in predicting clinical and patient outcomes in those with seronegative SS. Further research is necessary to determine the extent of its impact.

In summary, clinicians should be cautious of SS in patients who present with sicca symptoms or other clinical

features typical of SS, even if they do not have the typical SS autoantibodies. Therefore, it is important to objectively measure lacrimal function, for example, by conducting a Schirmer test, and to refer the patient for MSGB when necessary. The importance of early recognition, diagnosis, and management of SS is reflected by patients presenting with late and/ or serious complications, reduced quality of life, and increased health service utilization.

Informed Consent: Informed consent was taken from the patient.

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