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Atypical Autoantibodies in Patients with Primary Sjögren Syndrome: Clinical Characteristics and Follow-Up of 82 Cases

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OBJECTIVES To analyze the clinical characteristics, follow-up, and fulfillment of classification criteria for other systemic autoimmune diseases (SAD) in patients with primary Sjögren syndrome (SS) and atypical autoantibodies.

METHODS We studied 402 patients diagnosed with primary SS seen consecutively in our Department since 1994. We considered anti-DNA, anti-Sm, anti-RNP, antitopoisomerase1/Scl70, anticentromere (ACA), anti-Jo1, anti-neutrophil cytoplasmic antibodies (ANCA), anticardiolipin antibodies (aPL), and lupus anticoagulant as atypical autoantibodies. The patients were prospectively followed after inclusion into the protocol, focusing on the development of features that might lead to the fulfillment of classification criteria for additional SAD. As a control group, we selected an age–sex-matched subset of patients with primary SS without atypical autoantibodies.

RESULTS Eighty-two (20%) patients showed atypical autoantibodies (36 had aPL, 21 anti-DNA, 13 ANCA, 10 anti-RNP, 8 ACA, 6 anti-Sm, 2 anti-Scl70, and 1 anti-Jo-1 antibodies). There were 77 (94%) women and 5 (6%) men, with a mean age of 57 years. Patients with atypical autoantibodies had no statistical differences in the prevalence of the main sicca features, extraglandular manifestations (except for a higher prevalence of Raynaud's phenomenon, 28% versus 7%, $P = 0.001$), immunological markers, and in the fulfillment of the 2002 classification criteria, compared with the control group. After a follow-up of 534 patient-years, 13 (16%) of the 82 patients with atypical autoantibodies developed an additional SAD (systemic lupus erythematosus in 5 cases, antiphospholipid syndrome in 4, limited scleroderma in 3, and microscopic polyangiitis in 1) compared with none in the control group ($P < 0.001$).

CONCLUSIONS This study shows an immunological overlap (defined by the presence of autoantibodies considered typical of other SAD) in 20% of our patients with primary SS. However, the clinical significance of these atypical autoantibodies varies widely depending on the autoantibodies detected, with a broad spectrum of prevalence and clinical patterns of disease expression, and a specific predilection for association with some SAD in preference to others.

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Sjögren syndrome (SS) is a systemic autoimmune disease (SAD) that mainly affects the exocrine glands and usually presents as persistent dryness of the mouth and eyes due to functional impairment of the salivary and lacrimal glands (1). In the absence of an associated SAD, patients with this condition are classified as having primary SS (2). The histological hallmark is a focal lymphocytic infiltration of the exocrine glands, and the spectrum of the disease extends from an organ-specific autoimmune disease (autoimmune exocrinopathy) (3) to a systemic process with diverse extraglandular manifestations (4,5).

The overproduction of a wide variety of immunoglobulins including autoantibodies directed at specific nuclear or cytoplasmic antigens is a central etiopathogenic characteristic of primary SS. Nevertheless, the 1993 European Criteria (6) included the presence of 4 antibodies (antinuclear antibodies (ANA), rheumatoid factor (RF), Ro/SS-A, and/or La/SS-B) in the immunologic criteria and, in the recently proposed 2002 Criteria (7), only Ro/La has been included. However, patients with primary SS sometimes have autoantibodies considered characteristic of other SAD, although the clinical significance of this immunological overlap is not well established. Some studies have attributed the presence of some autoantibodies to the B-cell hyperactivity characteristic of primary SS (8,9), while the presence of other of these autoantibodies might have a predictive role for the development of additional SAD (10,11).

Abbreviations

ACR	American College of Rheumatology
aCL	anticardiolipin antibodies
ACA	anti-centromere antibodies
LKM-1	antiliver-kidney microsome antibodies type-1
AMA	antimitochondrial antibodies
ANA	antinuclear antibodies
PCA	anti-parietal cell antibodies
aPL	antiphospholipid antibodies
APS	antiphospholipid syndrome
SMA	antismooth muscle antibodies
CNS	central nervous system
LA	lupus anticoagulant
PAM	microscopic polyangiitis
MCTD	mixed connective tissue disease
MPO	myeloperoxidase
PR3	proteinase 3
RF	rheumatoid factor
SS	Sjögren syndrome
SEM	standard error of the mean
SAD	systemic autoimmune diseases
SLE	systemic lupus erythematosus
SSc	systemic sclerosis

The aims of this study were to analyze the clinical characteristics, follow-up, and fulfillment of classification criteria for other SAD in patients with primary SS and autoantibodies not included in the current SS classification criteria, to define the clinical relevance of this immunological overlap, and to suggest clinical guidelines for testing for these autoantibodies in primary SS.

Methods

Patients

We studied 402 patients diagnosed with primary SS seen consecutively in our Department since 1994. All patients fulfilled 4 or more of the preliminary diagnostic criteria for SS proposed by the European Community Study Group in 1993 (6) (including as mandatory criterion either positive immunological markers or salivary lip biopsy) and underwent a complete history and physical examination. Diagnostic tests for SS (rose bengal staining, Schirmer test, parotid scintigraphy, and salivary gland biopsy) were applied according to the recommendations of the European Community Study Group (6). Exclusion criteria for the diagnosis of primary SS were the coexistence of other SAD, preexisting hematological diseases, and hepatitis B virus, hepatitis C virus, or HIV infections. We considered the following as atypical autoantibodies:

- DNA antibodies (>20 UI/L by Farr's technique (12))
- Anti-Sm antibodies (ELISA)
- Anti-RNP antibodies (ELISA)
- Ani-Scl70 antibodies (ELISA)
- Anticentromere antibodies (ACA) (ELISA)
- Anti-Jo1 antibodies (ELISA)
- Antineutrophil cytoplasmic antibodies (ANCA) (staining patterns by indirect immunofluorescence, antigenic specificity by ELISA (13))
- Anticardiolipin antibodies (aCL) (IgG and IgM-aCL measured by ELISA (14))
- Lupus anticoagulant (LA) (coagulation assays (15))

The patients were prospectively followed after inclusion into the protocol, focusing on the development of clinical and/or laboratory features that might lead to the fulfillment of classification criteria for additional SAD. The diagnosis of associated SAD was based on the following criteria:

Systemic lupus erythematosus (SLE) according to the revised criteria of the American College of Rheumatology (ACR) (16);

Systemic sclerosis (SSc) by the ACR preliminary criteria (17);

Polymyositis-dermatomyositis by the Bohan and Peter criteria (18)