

The Sensitivity and Specificity of Autoantibodies to the Sm Antigen in the Diagnosis of Systemic Lupus Erythematosus

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Abstract

The anti-Sm test is thought to be specific for the diagnosis of systemic lupus erythematosus (SLE) and is one of the American College for Rheumatology (ACR) criteria for the classification of SLE. Locally, the sensitivity and specificity of this test for the diagnosis of SLE are unknown. We therefore aim to study the sensitivity and specificity of this test in our local context. A total of 1034 patient samples that were sent for routine testing of anti-Sm antibodies over a 30-month period, were included in the study. However, only 1031 patient samples were included in the final analysis as 3 casenotes were not traceable. Clinical diagnoses were obtained through a lupus database and chart review. Quantification of the anti-Sm antibodies was by the enzyme-linked immunosorbent assay (ELISA) technique. Positive anti-Sm test results were present in 165 samples, comprising 156 (94.5%) samples from lupus patients and 9 (5.5%) having diagnoses other than SLE. These diagnoses ranged from arthritis, overlap syndrome, Raynaud's phenomenon and cardiac-related diseases. The calculated sensitivity and specificity of the anti-Sm test, using a positive cut-off value of 20 units/ml, were 39.7% and 98.6%, respectively. If the positive cut-off value is raised to 30 units/ml, the specificity rises marginally to 99.5% but the sensitivity will drop by more than 10 percentage points to 27.2%. The anti-Sm test is not useful as a screening test for lupus but a positive result is highly specific for SLE.

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Introduction

The presence of multiple autoantibodies is the hallmark of systemic lupus erythematosus (SLE).¹ Many of these autoantibodies target nuclear antigens e.g. histones, Sm, RNP, SSA, SSB and dsDNA may give rise to a positive antinuclear antibody (ANA) test. Anti-dsDNA, biological false positive VDRL test and Anti-Sm are included as separate American College for Rheumatology (ACR) criteria for the classification of SLE² because of their specificity. Anti-Sm or anti-Smith autoantibodies specifically targets the Sm protein core, typically the B/B' or D proteins. Among Caucasians they are present in about 10% of lupus patients,³ while 25% of Chinese^{4,5} lupus patients have this autoantibody. Generally, because of its perceived specificity, the presence of this autoantibody has been regarded as indicating the presence of lupus or its imminent development. However in 1989, Abu-Shakrah and his co-workers^{6,7} reported 2 se-

ries of patients with anti-Sm / anti-RNP antibodies who did not present with symptoms related to SLE. Locally, the specificity and sensitivity of the anti-Sm test by the ELISA technique is unknown. With this background, we aim to determine the sensitivity and specificity of the anti-Sm test in local patients.

Materials and Methods

Blood Samples

Serum samples from Tan Tock Seng Hospital's patients that require routine detection of the anti-Sm antibody were sent to the Autoimmune Research Laboratory (ARL) since the second quarter of 1993. From January 1994 to December 1996, a total of 1034 patient samples were tested routinely for the presence of anti-Sm antibody. These form the study cohort as their serum samples, stored at -70°C, were available for rechecking if necessary. Patients who have a diagnosis other than

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lupus and have positive anti-Sm tests were retested in duplicates. For its routine service, the ARL participated in the United Kingdom National External Quality Assessment Scheme for detection of autoantibodies since its inception and has a regular rating score of good to ideal.

ELISA Technique

A commercial enzyme-linked immunosorbent assay (INOVA Diagnostics, USA) was used for the quantitative detection of the Sm antibodies in the patients' sera. Steps were performed according to the manufacturer's instruction. Briefly, affinity purified Sm antigen was bound to polystyrene microwell walls under conditions that will preserve it in its native state. Sequential steps involving the addition of diluted patient's sera, enzyme-labelled anti-human IgG conjugate and the chromogen were intersperse with 3 washing steps each to remove unbound antibodies. The colour intensity was measured at 450 nm after the reaction was stopped. The optical density value was then quantitated by comparison with the standards curve. For the ARL, a value of more than 20 units/ml was considered as significantly elevated. This represents 5 standard deviations above the mean value obtained from 40 healthy individuals.

Chart Review

The names and hospital registration numbers of patients with positive tests were compared with the names and hospital registration numbers on the list generated from the Department of Rheumatology and Immunology's lupus database. Chart reviews were done for those whose names did not appear on the lupus database's list so as to determine their diagnoses.

Sensitivity and Specificity

The sensitivity and specificity were calculated according to the following formulae (true-positives divided by the sum of true-positives and false negatives, and true-negatives divided by the sum of true-negatives and false positives, respectively). The values obtained were multiplied by a factor of 100. The positive and negative predictive values were also calculated according to the following formulae (true-positives divided by the sum of true-positives and false-positives, and true-negatives divided by the sum of true-negatives and false-negatives, respectively). The values obtained were also multiplied by a factor of 100.⁸

Results

Out of the 1034 patient names with hospital registration numbers, 3 casenotes were not traceable despite repeated efforts and were thus not included in the analysis. There were 165 positive anti-Sm tests among the 1031 patient samples (393 samples were from SLE

patients and 638 samples were from non-SLE patients). Of the 165 positive anti-Sm tests, 156 (94.5%) were from lupus patients (Table I). Among the 156 lupus patients with positive tests, 49 (31 %) had anti-Sm values between 20 and 30 units/ml. Nine (5.5%) of the 165 positive patient samples had non-SLE diagnoses. Their anti-Sm values ranged from 21 to 157 units/ml. Six (66.7%) of the 9 patients had anti-Sm values between 20 and 30 units/ml. Non-SLE diagnoses included arthritis, overlap syndrome, Raynaud's phenomenon and cardiac-related diseases (Table II). The calculated sensitivity, based on a positive cut-off value of 20 units/ml, was 39.7% and the specificity was 98.6%. The positive predictive value was 94.5% and the negative predictive value was 72.6%.

TABLE I: RESULTS OF THE ANTI-SM TEST IN SLE AND NON-SLE PATIENTS

	SLE	non-SLE	Total
anti-Sm +ve	156	9	165
anti-Sm -ve	237	629	866
Total	393	638	1031

+ve: positive test; -ve: negative test;
SLE: systemic lupus erythematosus

TABLE II: DIAGNOSES OF NINE NON-SLE PATIENTS WITH POSITIVE ANTI-SM TEST

Diagnosis	Anti-Sm (units/ml)
1. Arthritis (non-specific)	27
2. Recurrent miscarriages	157
3. Dilated cardiomyopathy	21
4. Reactive arthritis	34
5. Overlap syndrome with Raynaud's phenomenon	22
6. Rheumatoid arthritis with Raynaud's phenomenon	21
7. Subacute bacterial endocarditis	22
8. Systemic sclerosis with ischaemic heart disease	>160
9. Rheumatoid arthritis	22

SLE: systemic lupus erythematosus

Discussion

The anti-Sm test is highly specific for SLE in our cohort of patients. Nine patients with definite anti-Sm test do not have the complete features of SLE after 2 years of follow-up from the time that the test was performed. This finding shows that we may have underestimated the number of conditions (apart from lupus) that can give rise to positive anti-Sm. Abu-Shakrah and co-workers^{6,7} reported positive anti-Sm tests in patients with rheumatoid arthritis, myasthenia gravis, autoimmune thyroid disease and monoclonal gammopathy. With the exception of rheumatoid arthritis, the other conditions were not represented in our patients studied. Ideally, sera should be obtained from these patients and tested for anti-Sm antibodies. However, cost is a major con-

straining factor. Moreover, it would be more useful to determine the sensitivity and specificity of the test in the context where there is a suspicion of lupus disease. The anti-Sm test is relatively insensitive and hence many with lupus may be missed out if it is used as a screening test. However, it is a highly specific test with a specificity of 98.6% in "suspect" lupus. It is also noted that 6 of the 9 non-SLE patients have anti-Sm values between 20 and 30 units/ml. If the positive cut-off is arbitrarily raised to 30 units/ml, it would raise the specificity marginally to 99.5%. However, this would also lower the sensitivity of the test to 27.2%, a drop of more than 10 per cent. The percentage of positive tests (39.7%) among lupus patients seems to be high when compared to the figure of 25% obtained from previous studies on local lupus patients.^{4,5} Blood samples obtained from previous studies included patients with active and inactive diseases. The samples tested in the ARL are likely to come from patients who have newly diagnosed disease and therefore have active disease. This percentage is comparable to Japanese lupus patients who have a positive anti-Sm test rate of 36% in patients with active disease and 11% in patients with inactive disease.⁹ Finally, although the anti-Sm test is not useful as a screening test, its high specificity would mean that a positive test result must be closely monitored to ensure early detection of lupus.

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