Clinical Setting of Patients with Systemic Sclerosis by Serum Autoantibodies

U. PICILLO, S. MIGLIARESI, M.R. MARCIALIS, A.M. FERRUZZI, G. TIRRI

Summary  
Associations of antinuclear (ANA) and anticardiolipin (aCL) antibodies with clinical manifestations were analyzed in patients with systemic sclerosis (SSc).

We studied 105 SSc patients: 28 had limited cutaneous SSc (lcSSc) involving fingers; 36 had intermediate cutaneous SSc involving limbs and face; 33 had diffuse cutaneous SSc (dcSSc) involving the trunk; 8 had a sclerosis sine scleroderma. Clinical manifestations and instrumental and laboratory findings were considered to calculate a disease score. Serum anticientromere (ACA), anti-topoisomerase I (anti-topo I) antibodies, and aCL (of IgG/IgA/IgM classes) were investigated by conventional methods. ACA positive patients (n= 18), compared to ACA negative, showed higher prevalence of lcSSc (p < 0.001), lower prevalence of restrictive ventilatory defect (p=0.006), and lower disease score (p=0.008). Anti-topo I positive patients (n=70) showed lower prevalence of lcSSc (p=0.001) compared to anti-topo I negative. In aCL positive patients (n=27) widespread skin and visceral involvement occurred more frequently than in aCL negative. The association with myocardial ischemia or necrosis (p=0.010) was significant. Occurrence of ACA excluded the coexistence of anti-topo I (p < 0.001), and aCL (p=0.037). aCL positive patients showed higher disease score in comparison with ACA positive patients (p=0.003).

In conclusion ACA recognize patients with a mild disease, aCL in contrast to ACA are better than anti-topo I in recognizing the most severe pictures of SSc.

Key words  
Systemic Sclerosis, Antinuclear Antibodies, Anticentromere Antibodies, Anticardiolipin Antibodies, Antiphospholipid Antibodies, Disease Score of Systemic Sclerosis.

INTRODUCTION

Systemic sclerosis (SSc) is a systemic rheumatic disease, involving many internal organs besides the skin, particularly the gastrointestinal tract, lungs, heart, and kidneys. Raynaud's phenomenon and a widespread involvement of medium and small sized vessels are other prominent features (1). Presence of both cellular and humoral immunity abnormalities is a quite constant finding (2). As for humoral immunity, the presence of antinuclear antibodies (ANA) appears to be a serological marker of the disease correlating with different extensions of skin sclerosis and leading to the possibility of recognizing subsets of SSc patients with different clinical findings. In fact, the association of anti-topo I, (formerly named anti-Scl-70), with a diffuse skin sclerosis and with a poor prognosis, as well as the association of anticientromere antibodies (ACA) with a limited skin involvement and a better prognosis has been described (3,4).

Less attention has been given to antiphospholipid antibodies, even though these autoantibodies are associated with thrombosis and several vascular manifestations in other diseases such as systemic lupus erythematosus (SLE) (5-7), and primary antiphospholipid syndrome (8). Reports about anticardiolipin antibodies (aCL) in SSc are few and sometimes conflicting (9-12). We have recently detected the presence of aCL in a relevant percentage of SSc patients in our country and have also found the occurrence of a more severe disease in IgG- and IgA-aCL positive patients (13).

In the present study, we evaluated the prevalence and the association of some scleroderma-related ANA and aCL in our SSc series in an attempt to recognize distinct
groups of patients on the basis of the presence of these autoantibodies.

MATERIALS AND METHODS

Patients

One hundred and five unselected Italian patients (96 women, 9 men; age range 19-75 years, median 49), admitted to our Institute between 1983 and 1994, made up the study group. The duration of the disease from the first manifestation ranged from 1 to 44 years (median 10). The duration of the skin sclerosis ranged from 0.5 (for diffuse forms only) to 32 years (median 4); the patients with less skin involvement had skin sclerosis lasting at least 2 years. A complete clinical evaluation was carried out for each patient.

SSc subsets

Ninety-seven patients fulfilled the preliminary criteria of the American College of Rheumatology (ACR), formerly American Rheumatism Association) for the classification of SSc (14), and three subsets were distinguished on the basis of skin sclerosis extent, according to Giordano et al. (3): 28 patients had a limited cutaneous systemic sclerosis (lcSSc) involving the fingers, with minimal lesions on the face, neck, and armpits; 36 patients had an intermediate cutaneous systemic sclerosis (icSSc) with involvement of the forearms, legs, and face, and 33 patients had diffuse cutaneous systemic sclerosis (dcSSc) with involvement of the trunk. The 8 remaining patients showed a sine scleroderma systemic sclerosis (ssSSc) according to Rodnan et al. (15) and did not meet the ACR criteria (14). All the ssSSc patients suffered from Raynaud’s phenomenon, showed at least two other findings among digital pitting scars, telangiectasias, scleroderma-like involvement of esophagus, lungs, heart, kidneys, and joints, and scleroderma-related ANA.

Disease score

A standard protocol was employed to calculate a "disease score" for each patient (13). Cumulative clinical data registered up the time of serum collection were considered. Included items (with assigned values in parentheses) were: lcSSc (1); icSSc (2); dcSSc (3); digital pitting scars or ulcers (1); subcutaneous calcinosis (1); acroosteolysis, i.e. resorption of the tufts of the terminal phalanges of the fingers, (1); arthritis (1); muscular weakness and/or atrophy (1); muscle enzyme elevation (1); thrombosis (any site) (2); myocardial ischemia or necrosis (by electrocardiography and/or scintigraphy) (1); right ventricular hypertrophy (1); left ventricular hypertrophy (1); conduction defects (1); significant arrhythmias (1); pericarditis (1); dyspnea and/or cough and/or bibasilar rales (1); restrictive ventilatory defect (1); bibasilar pulmonary fibrosis (by X-ray or computed tomography scan) (1); creatinine clearance: 80-50 ml/minute (1); 50-20 ml/minute (2); < 20 ml/minute (3); scleroderma renal crisis (3); dysphagia (1); typical SSc esophageal dysmotility (1); esophageal stricture (1); malabsorption (2); colon saculation (2).

ANA testing

Patients’ sera were tested by indirect immunofluorescence on HEP-2 cells and patterns of fluorescence were identified by comparing with reference sera (3,16). double immunodiffusion in agarose as previously described (3) was employed to detect anti-topo I, anti-RNP, anti-Sm and anti-SS-B antibodies.

aCL measurement

A semi-quantitative ELISA for IgG-, IgA-, and IgM- aCL determination (REAADS Medical Products Inc., Westminster CO, USA) was employed (13,17). The normal ranges of aCL were established by testing sera from 50 normal Italian subjects (18). These sera showed aCL values at 50th percentile of 8.0 GPL, 15.2 APL and 5.2 MPL respectively and at 95th percentile of 23.4 GPL, 27.5 APL and 13.2 MPL respectively. Therefore aCL levels ≥24 GPL, ≥28 APL, and ≥14 MPL were considered positive. Levels of aCL were distinguished as multiples of these values into low (1.0-1.5x), medium (1.6-2.5x), and high (> 2.5x).

Statistical analysis

Fisher’s exact test in evaluating prevalence of clinical findings and Mann-Whitney U test in evaluating disease score and disease duration in independent groups were applied. Significance level was set at 0.05 and the critical values of p were adjusted for the number of comparisons according to Bonferroni (19). Therefore, values of p < 0.017 for the comparisons made in Table I and values of p < 0.044 for the comparisons made in Table II were considered significant.

RESULTS

Clinical findings in scleroderma patients distinguished according to the presence of ACA, anti-topo I, and aCL (of IgG and/or IgA and/or IgM classes) are reported in Table I.