Circulating soluble adhesion molecules in patients with systemic sclerosis: correlation between circulating soluble vascular cell adhesion molecule-1 (sVCAM-1) and impaired left ventricular diastolic function

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Abstract The objective of this paper is to investigate the relation between circulating soluble adhesion molecules and cardiac involvement, as assessed by echocardiography in patients with systemic sclerosis (SSc). Nineteen patients with SSc were submitted for assessment of serum levels of circulating soluble intercellular adhesion molecules (sICAM-1), and soluble vascular cell adhesion molecules-1 (sVCAM-1), and echocardiography. Abnormal left ventricular filling patterns (A/E/A ratio) were detected in ten patients (52.6%) with significant negative correlation with sVCAM-1 ($r = -0.484$, $P < 0.05$). It was also significantly correlated with age ($r = -0.791$, $P < 0.01$), age of onset ($r = -0.468$, $P < 0.05$), degree of dyspnea ($r = -0.687$, $P < 0.01$), and erythrocyte sedimentation rate (ESR) ($r = -0.489$, $P < 0.05$). Our findings suggest an important role for sVCAM-1 as a marker of disease severity and impaired left ventricular filling pattern in SSc.

Key words Systemic sclerosis · Adhesion molecules · Diastolic dysfunction

Introduction

Cardiac involvement is quite frequent in systemic sclerosis (SSc). It may be primary scleroderma heart disease, or secondary to either pulmonary interstitial or vascular involvement or to kidney disease [1]. Clinicopathological studies indicate that symptomatic heart involvement in patients with SSc predicts a poor prognosis [2]. Microvascular damage occurs in SSc and is associated with increased expression of endothelial adhesion molecules, including circulating soluble intercellular adhesion molecules-1 (sICAM-1) and circulating soluble vascular cell adhesion molecules-1 (sVCAM-1). It is suggested that the serial measurements of circulating adhesion molecule levels reflect disease severity in systemic sclerosis [3], and it is also suggested that they have a role in the inflammatory and fibrotic processes underlying SSc [4].

The present paper highlights the relationship between sICAM-1 and sVCAM-1, and the cardiac involvement as assessed by echocardiography in patients with SSc.

Methods

Patients

Nineteen non-smoking patients affected by SSc followed up in the Department of Rheumatology and Rehabilitation, Kasr El-Eini Hospital, from April 1998 to April 1999 (18 women, mean age 38.1 ± 14.6 years, range 14–60 years, mean age of onset 29.4 ± 15.8 years, mean disease duration 8.2 ± 7.7 years). All patients followed the American Rheumatism Association Preliminary Criteria for Diagnosis of SSc [5]. Twenty normal subjects (mean age 38.9 ± 15.9 years) served as controls for sICAM-1 and sVCAM-1 measurements.

Eleven patients were affected by diffuse scleroderma (dSSc) based on the extension of the skin tethering to sites proximal to the elbow [5, 6]; mean age 36.5 ± 16.3 years, mean age of onset 27.5 ± 18.8 years, mean duration 8.2 ± 6.2 years. Eight patients were affected by a limited form of the disease (ISSc); mean age 40.3 ± 12.7 years, mean age of onset 32.5 ± 4.0 years, and mean duration 8.3 ± 9.9 years.

All patients underwent a complete clinical examination, including evaluation for gastrointestinal, pulmonary, cardiac, renal,
or muscle involvement. The grade of dyspnea (if present) was determined based on Sherwood Jones Classification [7]: 1a = able to do housework or job with moderate difficulty, 1b = carry out job or housework with great difficulty, 2a = confined to chair or bed but able to get up with moderate difficulty, 2b = confined to chair or bed but able to get up with only great difficulty, 3 = totally confined to chair or bed, and 4 = moribund. Routine laboratory examinations were performed, including a complete blood picture, erythrocyte sedimentation rate (ESR), and liver and kidney functions, in addition to creatinine phosphokinase (CPK), lactate dehydrogenase (LDH), and serum aldolase measurements. Anti-nuclear antibodies (ANA) were detected by immunofluorescence. Pulmonary function testing and esophageal manometric studies were carried out on all patients.

Doppler echocardiography

Two-dimensional Doppler echocardiography techniques were applied to all patients. Imaging was performed with Hewlett-Packard Sonos 1000, equipped with 2.5 and 3.5 MHz phased pulsed array transducers. Doppler studies were performed for assessment of the mitral flow and measurements of: maximal early diastolic flow velocity (peak E, m/s), maximal late diastolic flow velocity (peak A, m/s), and E/A ratio. Guided with color flow imaging, pulsed wave (PW) was used to detect and quantitate the magnitude of mitral and tricuspid regurgitation (MR and TR, respectively). In the presence of TR, continuous wave (CW) Doppler was used to estimate the pulmonary artery systolic pressure. First, the transtricuspid systolic pressure gradient (TSPG) was estimated according to the modified Bernoulli equation [8]; to calculate pulmonary artery systolic pressure, 10 mmHg (estimated systolic right atrial pressure) was added to TSPG. Pulmonary systolic hypertension was defined as >35 mmHg. If no TR was detected, pulmonary artery systolic pressure was presumed normal.

Serum levels of sICAM-1 and sVCAM-1

Serum levels of sICAM-1 and sVCAM-1 were estimated by using solid phase sandwich enzyme-linked immunosorbent assay (ELISA) [9]. The kits were provided by Biosource International Cytoscreen (Calif., USA). Serum levels were more than 2 SD greater than the mean level in the normal control subjects were regarded as elevated.

Skin tethering assessment

A semi-quantitative scoring system was used to evaluate skin involvement [10]. The body was divided into ten regions (face, chest, back, abdomen, upper arms, forearms (including wrists), hands, thighs, legs, and feet). The degree of skin involvement in each region was rated as follows: 0 = normal skin, 1 = mildly thickened skin, 2 = moderately thickened skin, and 3 = hidebound skin. The highest possible score was 30.

Statistical analysis

Data were reported as mean ± SD. Student’s t-test and chi-squared tests were used when appropriate. Correlation analysis was performed utilizing Pearson’s correlation. Correlation between continuous variables was evaluated by linear regression analysis.

Results

General features of all patients are shown in Table 1. The difference between patients with dSSc and those with ISSc was nonsignificant concerning Raynaud’s phenomenon (92.9% vs 100%); esophageal motility (45.5% vs 37.5%); systemic hypertension (27.3% vs 37.5%); telangiectasia (45.5% vs 37.5%); dyspnea score (2.0 ± 1.0 vs 1.8 ± 0.5); arthralgia (63.6% vs 87.5%); muscle tenderness (27% vs 37.5%); forced vital capacity, FVC% (72.6 ± 20.4 vs 64.3 ± 5.8); and diffusion capacity for carbon monoxide, DLco% (73.4 ± 35.1 vs 69.9 ± 23.1), respectively. Skin score mean of dSSc was 16.7 ± 6.5 and that of ISSc was 10.5 ± 5.1 with P < 0.05. One patient with dSSc had mild renal insufficiency with a creatinine level of 2.9 mg/dl. Drug treatment included corticosteroids (four patients), d-penicillamine (eight patients), methotrexate (two patients), and calcium channel blockers (12 patients).

Doppler echocardiography

Pulmonary artery systolic pressure was elevated in two patients (10.5%) who both had dSSc.

Abnormal left ventricular filling pattern (E/A ratio) was detected in ten patients (52.6%), six with dSSc (54.6%), with no statistical significant difference between disease subgroups (mean E/A ratio 1.2 ± 0.1 for dSSc vs 1.2 ± 0.2 for ISSc). Two cases of all patients (dSSc and ISSc) had TR (10.5%) and three cases of patients with dSSc had MR (15.8%).

A significant negative correlation was observed between E/A ratio and each of sVCAM-1 (r = -0.484, P = 0.05) (Fig. 1a), age (r = -0.791, P < 0.01), age of onset (r = -0.608, P < 0.01) (Fig. 1b), and ESR (r = -0.489, P < 0.05).

Serum levels of sICAM-1

Serum levels of sICAM-1 were elevated significantly in patients when compared with controls (mean of patients 1656.8 ± 562.9 ng/ml vs mean of control 638.6 ± 415.4 ng/ml) with P < 0.0001. The difference between the disease forms was non-significant (1667.1 ± 697.9 ng/ml for dSSc vs 1641.2 ± 344.5 ng/ml for ISSc). No significant correlation was observed between levels of sICAM-1 and sVCAM-1.

Serum levels of sVCAM-1

Serum sVCAM-1 levels were significantly elevated in patients compared with controls (mean of patients 2716.1 ± 1569.3 ng/ml vs 665.0 ± 214.2 ng/ml of controls) with P < 0.0001. The cut-off value (2 SD above the mean in the control subjects) was set at 1093.4 ng/ml. Elevated serum levels of sVCAM-1 were found in 16 patients (84.2%). The difference between the disease forms concerning serum sVCAM-1 levels was non-significant (2459.6 ± 1707.6 ng/ml for dSSc vs 3068.8 ± 1386.1 ng/ml for ISSc). In addition to the diastolic dysfunction, sVCAM-1 was correlated signifi-