Egyptian Journal of Chest Diseases and Tuberculosis (2015) 64, 237–241

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The Egyptian Society of Chest Diseases and Tuberculosis

Egyptian Journal of Chest Diseases and Tuberculosis

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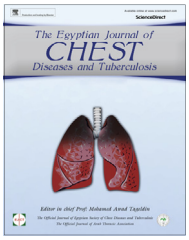

ORIGINAL ARTICLE

Interleukin-6 in systemic sclerosis and potential correlation with pulmonary involvement

Maha Yousif [a,*], Rehab Habib [b], Heba Esaely [c], Rabab Yasin [b], Ahmed Sonbol [d]

[a] *Chest Department, Faculty of Medicine, Minoufiya University, Egypt*
[b] *Radio-diagnosis Department, Faculty of Medicine, Minoufiya University, Egypt*
[c] *Rheumatology Department, Faculty of Medicine, Minoufiya University, Egypt*
[d] *Clinical Pathology Department, Faculty of Medicine, Minoufiya University, Egypt*

Received 5 October 2014; accepted 29 October 2014
Available online 29 November 2014

KEYWORDS

Systemic sclerosis;
Interleukin-6;
High resolution CT;
Interstitial lung disease;
Cytokines

Abstract *Background:* A progressive pulmonary involvement is frequent in systemic sclerosis and it is the leading cause of morbidity and mortality. IL-6 has been implicated in the pathogenesis of systemic sclerosis via stimulation of fibroblasts to produce excess collagen and glycosaminoglycan. Specific correlation between IL-6 and lung involvement have not been found yet.

Aim: To study the possible correlation between lung involvement (assessed by spirometry and HRCT abnormalities) and the serum level of IL-6.

Subjects and methods: 20 patients with scleroderma compared with 20 matched volunteers as control group. All participants underwent spirometry, HRCT scan and serum IL-6 measurements. HRCT signs were scored according to Warrick et al. score for systemic sclerosis.

Results: Patients showed a statistically significant reduction in FVC%, FEF 25–75% and significantly higher ESR and IL-6 compared to control. There was a highly significant positive correlation between the total HRCT score and serum IL-6.

Conclusion: Serum IL-6 could be a marker of the degree of pulmonary involvement in patients with systemic sclerosis.

Introduction

Systemic sclerosis (SS) is a diffuse connective tissue disease of unknown etiology, characterized by skin and visceral fibrosis, vascular dysfunction, and circulating autoantibodies [1]. Pulmonary involvement is frequent in SS. It is reported in 70% [2] to 100% [3] of patients in autopsy series.

Several cytokines and chemokines have been implicated in the induction of fibrosis, but a definitive relationship between specific cytokines and some organ involvement has not been

Abbreviations: IL-6, interleukin-6; SS, systemic sclerosis; HRCT, high resolution CT; PFT, pulmonary function test; FVC, forced vital capacity; FEV1, forced expiratory flow in the first second; FEF 25–75%, forced expiratory flow 25–75%; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; Anti Scl-70, anti scleroderma-70; DLCO, diffusing capacity; TLC, total lung capacity

* Corresponding author at: Tel.: +20 1008818827; fax: +20 482233521.
E-mail addresses: drmahayousif@gmail.com (M. Yousif), rehab_habib77@yahoo.com (R. Habib), hebaesaily@yahoo.com (H. Esaely), rabab_yasin@outlook.com (R. Yasin), ahmed_sonbolmmm@yahoo.com (A. Sonbol).

Peer review under responsibility of The Egyptian Society of Chest Diseases and Tuberculosis.

http://dx.doi.org/10.1016/j.ejcdt.2014.10.004

established yet [4]. IL-6, one of the pro-inflammatory cytokines, has been implicated in the pathogenesis of SS. IL-6 expression is reportedly high in both the skin and serum of SS patients [5], and its elevation depends on the skin score [6].

Open lung biopsy remains the gold standard to diagnose interstitial lung disease, high resolution CT (HRCT) is considered to be the reference among the noninvasive procedures. It allows very precise analysis of lung parenchyma, with the advantage of assessing lung volumes [7]. Interstitial signs on HRCT are not equal in significance. Honeycombing, for example, has a worse prognosis than ground-glass appearance [8]. Warrick et al. [9] have defined a score based on the criteria of type and extent of HRCT signs in SS patients. The aim of this study is to study the possible correlation between lung involvement {assessed by spirometry and HRCT abnormalities} and the serum level of IL-6 in SS patients.

Patients and methods

Twenty patients (6 males and 14 females) with SS were recruited from the rheumatology outpatient clinic in Minoufiya University Hospital during the period from Oct 2012 to Oct 2013 and 20 age and sex- matched apparently healthy control subjects. All patients fulfilled the criteria proposed by the American College of Rheumatology [10]. None of the patients had recent symptoms or signs of lower respiratory infection at the time of the study. Known histories of asthma, allergic alveolitis, or exposure to organic dusts were exclusion criteria. Informed consent and ethical approval from Minoufiya University Hospital Ethics Committee were obtained from all participants before enrollment.

Pulmonary function test

Pulmonary function tests (PFT) were done for all the patients in the pulmonary function test unit in Minoufiya University Hospital using spirometer (Quark PFT3, COSMED, Italy) All measurements were performed according to the American Thoracic Society recommendations and expressed as percent of predicted values based on age, sex and height. Clinically significant restrictive lung disease was defined when an abnormal FVC with normal FEV1/FVC was observed [11].

HRCT scanning

All participants underwent a HRCT scan of the chest. HRCT scans were read by two independent radiologists in random order, without knowledge of the results of the other's findings. A consensus was obtained in all cases after a common third reading. The parenchymal abnormalities identified on HRCT were coded and a score was defined according to Warrick et al. [9]. A point value was assigned to each abnormality (ground-glass appearance, (1) irregular pleural margins, (2) septal/sub-pleural lines, (3) honeycombing, (4) sub-pleural cysts and (5)). For each patient, a ''severity of disease'' score was obtained by adding these point values. An ''extent of disease'' score was obtained by counting the number of bronchopulmonary segments involved for each abnormality: 1–3 segments scored 1; 4–9 segments scored 2; >9 segments scored 3. Finally, severity of disease and extent of disease scores were added to form a total HRCT score, with a possible range of 0–30.

IL-6

Serum IL-6 levels were examined by ELISA, as described by manufacturer (Biosource, Nivelles, Belgium); fasting venous blood samples were taken from all participants when HRCT or PFTs were carried out.

Statistical analysis

Data were analyzed by the SPSS version 13.0 statistical package. Categorical and quantitative variables were respectively described as numbers, percentage (%) and mean ± standard deviation (SD). Between-group comparisons were performed using Student's t test for variables with a normal distribution and the Mann–Whitney U-test for variables with a non-normal distribution. Correlation between variables was calculated by Pearson correlation coefficient. P values < 0.05 were considered statistically significant.

Results

This study was conducted on 20 patients with SS (6 males and 14 females) and another 20 control subjects (8 males and 12 females). The FVC% and FEF 25–75% were significantly lower in the patients compared to controls. There was no significant difference between the two groups regarding age, sex and FEV1/FVC Table 1.

There were significantly higher values of ESR, CRP, Anti Scl-70 and IL-6 in patients compared to controls Table 2.

In the studied patients, there was a significantly positive correlation between serum IL-6 level and each of CRP, Anti Scl-70 and HRCT score. Table 3, Figs. 1–3.

Discussion

Several lines of evidences indicate that SS presents deregulated production of cytokines implicated in vascular damage and fibrosis, but their relationship with clinical findings is still unclear. We studied the possible correlation between lung involvement (assessed by PFT and HRCT abnormalities) and the serum level of IL-6. We found significantly higher levels of serum IL-6 in patients with SS compared to controls (Table 2).Moreover, serum IL-6 correlated positively with Anti Scl-70 (Table 3, Fig. 3). This goes in agreement with several studies [5,12–14]. IL-6 is a pleiotropic cytokine with multiple biological effects on immune regulation, haematopoiesis, inflammation, oncogenesis [15–20]. Several authors [12,13,21] have demonstrated increased production of IL-6 by fibroblasts in SS patients. Duncan et al. [22] study showed furthermore increased production of collagen and glycosaminoglycans, hyaluronic acid and chondroitin-4/6-sulfates from human dermal fibroblasts induced by IL-6 suggesting a role for IL-6 in promoting fibrosis, and increased levels of IL-6 have been reported in the serum, bronchoalveolar lavage, and skin biopsies of patients with SS [5,18,21,23]. Moreover, Lung fibrosis induced by irradiation or bleomycin therapy is attenuated in IL-6 gene knockout mice [24].

The present study demonstrated a highly significant positive correlation between serum IL-6 and CRP (Table 3, Fig. 2). This is in agreement with Alegre-Sancho et al. [25]