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Conventional markers in determination of activity of sarcoidosis

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ABSTRACT

Aim and background: Currently, there are no objective criteria to determine sarcoidosis activity. The present study aimed to discover a sensitive serum marker that would determine the activity of sarcoidosis and can be used during disease follow-up.

Methods: Forty-eight patients with sarcoidosis and twenty healthy volunteers as a control group were included in the study. On their control visits, the patients were divided into active and inactive groups based on their clinical, physiological, and radiological status. Angiotensin converting enzyme (ACE), adenosine deaminase (ADA), total IgE (T-IgE), C-reactive protein (CRP), serum amyloid-A (SAA), and soluble interleukin-2 receptor (sIL2R) serum levels and classical findings of activity were compared, and the utilization of these parameters as markers of activity was investigated.

Results: Thirty-nine cases were female (female/male: 39/9) and the mean age was 44.29 ± 10.9 years. Thirty-seven cases were active and 11 cases were inactive. Serum ACE, ADA, sIL2R, and SAA levels were significantly higher while T-IgE levels were lower in the sarcoidosis cases. A comparison of the markers between active and inactive cases showed that only SAA was significantly higher ($p < 0.001$). sIL2R was elevated in cases with extra-pulmonary involvement ($p < 0.014$). The area under the curve value was rather high for ADA (0.98 CI: 0.96–1.0); it also had high sensitivity (93.8%) and specificity (100%), and therefore had the highest diagnostic value (96.6%).

Conclusion: The current study showed that SAA will be helpful for the activity of sarcoidosis, IL2R measurement in exploring the extra-pulmonary organ involvement.

1. Introduction

Sarcoidosis is an inflammatory granulomatous disease with unknown etiology and may affect various organs in addition to the lungs. It generally has a good prognosis; however, it may have a poor course leading to pulmonary fibrosis in some patients. There are currently no accurate criteria that can predict the course of the disease or that can be used during follow-up. Therefore, it is important to determine the disease activity in sarcoidosis in order to select the correct treatment option or even partially predict the course of the disease. Active sarcoidosis implicates the persistence of T-lymphocyte and macrophage associated inflammatory processes, the presence of granulomas and the possibility of the disease progression towards fibrosis [1]. However, it should be considered that some conditions such as Löfgren syndrome, which shows that the disease is active, have good prognosis or majority of the active patients may have spontaneous regression. Several diagnostic techniques and markers including angiotensin converting enzyme (ACE), adenosine deaminase (ADA) levels, gallium scintigraphy, total IgE, neopterin, and increased lymphocyte count in the bronchoalveolar lavage (BAL) fluid have so far been investigated to assess the activity of sarcoidosis [1–3]. It has been recently discussed that C-reactive protein (CRP), serum YKL-40, interleukin-18 (IL-18), serum amyloid A (SAA), and soluble interleukin-2 receptor (sIL2R) can also be used in the follow-up of patients with sarcoidosis [4–6].

Abbreviations: ACE, angiotensin converting enzyme; ADA, adenosine deaminase; CRP, C-reactive protein; T-IgE, total IgE; SAA, serum amyloid-A; sIL2R, soluble interleukin-2 receptor; BAL, bronchoalveolar lavage; TNF-α, tumor necrosis factor-α; EN, erythema nodosum; FEV1, forced expiratory volume 1st second; FVC, forced vital capacity; DLCO, carbon monoxide diffusing capacity; FOB, Fiberoptic bronchoscopy.

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ACE is the most commonly used laboratory test in sarcoidosis; it is important for the diagnosis and prognosis of sarcoidosis. However, it can be insufficient in some cases [1]. ACE levels may be elevated in other diseases as well, and also involves several allelic polymorphisms [7]. ADA is a product of purine metabolism and it is one of the determinants of cellular immunity, and measuring the levels of ADA was shown to be superior to the markers such as neopterin and ACE in differentiating the active and inactive diseases [8]. Sarcoidosis involves monocyte–macrophage activation against an inflammatory agent and cytokines such as tumor necrosis factor-α (TNF-α) and interleukin (IL) are produced [9]. IL-1 and IL-6 stimulated the production of acute phase proteins such as CRP and SAA. CRP is designated as a stable marker of systemic inflammation [10,11]. IL-1 and IL-6 released from the active monocyte–macrophages also stimulate the production of IL-2. IL-2 production causes activation of the T-cells. Active T-cell surfaces possess IL-2 receptors (55-kDa/75-kDa heterodimer) and the 55-kDa chain is called the soluble IL-2 receptor (sIL2R). It has been reported that sIL2R increases in the cases of active sarcoidosis [6,8].

The current study assessed the consistence of serum markers including ACE, ADA, T-IgE, CRP, SAA, and sIL2R with the clinical, physiological, and radiologically determined disease activity and explored whether these markers can be used to objectively determine the activity.

2. Methods

2.1. Patient population

Among 210 patients who had been monitored for at least six months at an outpatient clinic with the diagnosis of sarcoidosis, 48 voluntary cases who attended a polyclinic visit within the five-month time interval were consecutively included in the study. Demographic characteristics, pulmonary function test results, diagnostic methods, treatment status, and disease recurrences, if any, that have occurred since the initial diagnoses were recorded. Twelve cases were on treatment; however, no separate analysis was performed for the group under treatment since the study objective was the determination of active patients irrespective of treatment status. Twenty healthy, non-smoking individuals were included as the control group. Informed consent forms were obtained from all subjects that were included in the study. The study was approved by the Istanbul Goztepe Training and Research Hospital Ethics Committee (08.06.2007/38/A).

2.2. Determining the activity

With respect to disease activity, the patients were evaluated based on clinical, pulmonary function tests and radiological findings compared to the previous check-ups. The disease was defined as active in the presence of at least one of the below criteria [11,12].

2.2.1. Clinically

1. Presence of erythema nodosum (EN);
2. Arthritis;
3. Presence of dyspnea. Degree of dyspnea was evaluated according to the English Medical Research Council (MRC) Dyspnea Scale [13];
4. Recently appearing extra-pulmonary organ involvement.

2.2.2. With respect to pulmonary functions

1. At least a 15% difference in forced expiratory volume 1st second (FEV1) and forced vital capacity (FVC) values according to the pulmonary function tests performed at three month intervals;
2. At least a 10% difference in the carbon monoxide diffusing capacity (DLCO) value.

2.2.3. Radiologically

1. Appearance of a new lymph node;
2. Doubling in the volume of an already existing lymph node or regression;
3. Newly developing diffuse interstitial and/or alveolar type radiological pattern.

2.3. Diagnosis

In addition to the appropriate clinical and radiological findings, sarcoidosis diagnosis was based on showing histopathologically non-caseating granulomas, negative results in the examinations for tuberculosis and fungus (direct examination, culture), and the exclusion of other granulomatous diseases in the biopsies obtained from one or more organs. In the cases that did not provide a biopsy for histological diagnosis and/or in the cases with Löfgren syndrome, the diagnosis was made based on clinical and radiological consistency and the exclusion of other diseases, as well as the relevance of gallium scintigraphy findings and the exclusion of any non-sarcoidosis diseases during the follow-up. Fiberoptic bronchoscopy (FOB) was performed in all cases. Echocardiography, abdominal ultrasound, and skin and eye examinations were performed on all patients. Radiological classification was completed based on the Siltzbach classification [14]. Serum markers were assessed in the sarcoidosis cases and healthy volunteers, and their diagnostic values were investigated.

2.4. Treatment

Asymptomatic stage I cases were not treated unless they had extra-pulmonary involvement. Stage II and III cases with mild or moderate symptoms were closely monitored and the possibility of spontaneous remission was considered. Cases that were symptomatic, had impaired pulmonary function tests, had lung involvement with radiologically widespread infiltration, or extra-pulmonary organ involvement with a treatment indication were treated. Corticosteroid treatment regimen was administered based on the six-step treatment plan of Judson [15]. Q16

2.5. Follow-up

The patients who began to receive corticosteroid treatment after diagnosis were clinically and radiologically followed-up with monthly

Table 1
Demographical characteristics of the sarcoidosis cases.

	n	%
Number of patients	48	
Female/male	39/9	81/19
Age (mean)	44.29 ± 10.90	
Smoker/nonsmoker	11/37	23/77
Diagnostic method		
Biopsy (FOB, skin, parotid)	23	47.91 Q1
Mediastinoscopy	15	31.25
Clinical radiological	5	10.42 Q2
Ga scintigraphy + clinical radiological	5	10.42 Q3
Stage		
1/2/3/4	25/17/6/0	52.1/35.4/12.5/0
Pulmonary function parameters		
FEV1 (mean) %	83.12	
FVC (mean) %	87.26	
FEV1/FVC (mean) %	81.60	
DLCO (mean) %	80.80	
Symptoms		
EN/arthritis/dyspnea	1/0/28	2.1/0/58.8
MRC		
0/1/2/3/4	28/17/3/0	58.3/35.4/6.3/0

EN: erythema nodosum, FEV1: forced expiratory flow volume 1st second, FVC: forced vital capacity.

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