Serum ACE Level in Sarcoidosis Patients with Typical and Atypical HRCT Manifestation

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Summary

Background: Sarcoidosis is an inflammatory disease that affects multiple organs. Before widespread use of computed tomography (CT), the severity of sarcoidosis was assessed based on chest X-ray abnormalities. HRCT can distinguish between active inflammatory changes and irreversible fibrosis. In this study, we analyzed different ACE levels in 148 patients diagnosed with sarcoidosis.

Material/Methods: We categorized these patients based on their HRCT results into four groups: 1) patients diagnosed with chronic disease; 2) patients diagnosed with non-chronic disease; 3) patients who exhibited typical HRCT changes; and 4) patients who exhibited atypical HRCT changes. Afterward the mean ACE level of each group was calculated and compared.

Result: The HRCT scans of chronic sarcoidosis patients tended to show more atypical sarcoidosis patterns. Moreover, there was a reverse correlation between chronicity and ACE level (P-value <0.05).

Conclusions: HRCT is another modality which would be useful when the diagnosis of sarcoidosis is not definite.

MeSH Keywords: Angiotensin-Converting Enzyme Inhibitors • Four-Dimensional Computed Tomography • Sarcoidosis

Background

Sarcoidosis is an inflammatory disease that affects multiple organs, has undetermined origins, and is associated with non-caseating granuloma-epithelioid cells and lymphocytic alveolitis [1,2].

The areas affected by this disease in 90% of sarcoidosis patients are the hilar and mediastinal lymph nodes and the pulmonary parenchyma [3].

Although pulmonary and constitutional symptoms are prevalent in these patients, 50% of them are asymptomatic and are diagnosed unexpectedly after abnormalities are discovered in chest X-rays [4,5].

Before widespread use of computed tomography (CT), the severity of sarcoidosis, based on chest X-ray abnormalities, was categorized according to the Kveim-Siltzbach method [6]. CT scanning, particularly high-resolution computed tomography (HRCT), is very effective at detecting minor pulmonary parenchymal abnormalities at the first stages of sarcoidosis [4,7]. Moreover, HRCT can distinguish between active inflammatory changes and irreversible fibrosis. For example, findings such as parenchymal nodules, ground-glass opacity, and alveolar opacity are indicative of granulomatous inflammation, which is usually reversible after therapy [8]. In contrast, abnormalities such as honeycomb changes, bullae formation, and thick septal bronchiectasis bands are indicative of irreversible fibrosis [9,10] (Figures 1–3).

A reliable way to diagnose sarcoidosis is by measuring serum markers. Angiotensin-converting enzyme (ACE), which is produced by epithelioid cells derived from activated macrophages, is a known marker for sarcoidosis. ACE level is correlated with the amount of whole-body...
granuloma (not ones found in the lungs only) [11] and disease severity [12,13]. ACE level is elevated in other granulomatous diseases, such as leprosy [15] and histoplasmosis [16], and in non-granulomatous diseases, such as hyperthyroidism [16,17] and lymphoma [18].

One difficulty that arises in diagnosing sarcoidosis according to pathologic specimen analysis is the similarity in pathologic appearance between it and other granulomatous diseases, which also have a high level of ACE. As such, finding a relationship between the radiologic pattern of the disease and the ACE level is of great value as a diagnostic method when the ACE level and pathologic analysis are not conclusive.

In this study, we analyzed different ACE levels in 148 patients diagnosed with sarcoidosis. We categorized these patients based on their HRCT results into four groups: 1) patients diagnosed with chronic disease; 2) patients diagnosed with non-chronic disease; 3) patients who exhibited typical HRCT changes; and 4) patients who exhibited atypical HRCT changes.

Material and Methods

In this study, we examined the hospital or clinic documents of 148 patients diagnosed with sarcoidosis, according to the European Respiratory Society/American Thoracic Society/World Association of Sarcoidosis and Other Granulomatous Diseases guidelines [7]. These patients were referred to Masih Daneshvari Hospital in Tehran, Iran, between 2011 and 2014. They were either patients in the pulmonary ward or patients referred to outpatient clinics for a follow-up. Written and informed consent statements were obtained from all patients.

All patients had sarcoidosis with pulmonary involvement. Patients were excluded from the study if they smoked or had a coincident chronic fibrotic pulmonary disease such as hyper-reactive pneumonia or interstitial lung disease, or another systematic disease that leads to an increase in ACE levels (such as chronic obstructive pulmonary disease, pulmonary cancer, or nephrotic syndrome).

Patient information, including age, sex, and last ACE level, was recorded. The patients’ HRCT scans were examined by two experts with consensus. Abnormalities, such as honeycomb changes, bullae formation, and tractional bronchiectasis fibrotic band, are usually suggestive of disease chronicity, so the patients whose scans showed such abnormalities were categorized in the chronic group, whereas patients whose scans showed reversible changes such as parenchymal nodules, ground-glass opacities, and alveolar opacity were categorized in the non-chronic group [9,10].

In contrast, symmetrical prehilary, mediastinal lymphadenopathy, and perilymphatic micronodules are representative of typical sarcoidosis changes (Figure 3), and...
macronodules, lung mass, miliary opacities, and linear opacities are considered as atypical manifestation (Figure 1). Afterwards, the mean ACE level of each group was calculated and compared.

Statistical analysis

Statistical analysis was performed using SPSS software (version 18). Descriptive analysis was performed to show quantitative variables such as mean (standard deviation) and categorical variables such as frequency (%). Categorical data were compared using the chi-square equation. Statistical significance was considered to be less than 0.05.

Results

This study included one hundred and forty-eight sarcoidosis patients. The patients’ mean age was 46 years (standard deviation, 16) with a range of 17–75. There were 86 (58%) women and 62 (42%) men. The patients’ mean ACE level was 68 U/L (standard deviation, 15) with a range of 3–259.

As shown in Table 1, patients were categorized based on chronicity, typical/atypical changes, and ACE level. ACE level was divided into two groups, with 50 U/L as the cut-off point [19].

Among 127 patients with non-chronic disease, 82 (65%) had typical HRCT manifestations of sarcoidosis, whereas among 21 patients with chronic disease, only seven (33%) had typical HRCT presentations. This relationship between HRCT manifestation and disease chronicity was statistically significant ($P=0.007$).

The correlation between ACE level and chronicity and form of HRCT manifestation is shown in Table 2.

Discussion

In this study, we assessed the ACE levels and HRCT scans of 148 sarcoidosis patients. According to our results, there is a relationship between disease chronicity and HRCT patterns. The HRCT scans of chronic sarcoidosis patients tended to show more atypical sarcoidosis patterns. Also, there was a reverse correlation between chronicity and ACE level. Furthermore, no statistically significant difference existed between typical and atypical HRCT presentation based on a patient’s ACE level.

ACE is a serum marker that is increased in sarcoidosis. ACE is produced by epithelioid cells that are derived from recently-activated macrophages in granulomas; thus, ACE is an appropriate representative of whole-body granuloma [11].

KI-6 and sIL-2R are two other serum markers that are mainly increased in radiographic higher-stage sarcoidosis patients. Also, these markers are particularly indicative of disease progression and lymphocytic alveolitis changes [8,11,20,21].

Investigators have shown that there is no correlation between ACE level and sarcoidosis prognosis [22] and this marker demonstrates an overall granuloma amount in whole rather than lung involvement [23].

Other studies that analyzed ACE level increase in other granulomatous and non-granulomatous diseases reported the sensitivity and specificity of this marker in diagnosing sarcoidosis to be between 40% and 100%, and 83% and 99%, respectively [24,25]. Moreover, no difference in ACE levels has been reported between sexes and between different ages [26,27]. Many studies have shown that patients with higher ACE levels suffer from a more severe sarcoidosis [13,24,28,29]. Silverstein et al. [30] showed that there was a reverse relationship between sarcoidosis chronicity and ACE level, which is what we found as well.

Studies have shown [28,31,32] that prednisolone therapy leads to a reduction in ACE levels; therefore, it is recommended that patients stop taking prednisolone 2–4 weeks prior to ACE level measurement. Since our study was conducted retrospectively, one limitation was that the last ACE level of some patients was measured during prednisolone therapy.

Table 1. Patient categorization based on ACE level and HRCT presentation.

| No. (%) | ACE | Chronicity (No.)* | Form (No.)** |
|---------|-----|------------------|--------------|
|         | >50 | Chronic (21)     | Typical (89) |
|         | 86  | 8                | 56           |
|         | <50 | Non-chronic (127)| Atypical (59)|
|         | 62  | 13               | 30           |

* The correlation between ACE level and disease chronicity based on patients’ HRCTs is statistically significant ($p$-value=0.045); ** There was no statistically significant difference between typical-atypical HRCT presentations categorized based on patients’ ACE level ($p$-value=0.145).

Table 2. ACE level correlation with disease chronicity and typical-atypical pron HRCT.

| No. (%) | ACE level | Chronicity (No.)* | Form (No.)** |
|---------|-----------|------------------|--------------|
|         | >50       | Chronic (21)     | Typical (89) |
|         | <50       | Non-chronic (127)| Atypical (59)|
|         |           | 8                | 56           |
|         |           | 13               | 30           |

* The correlation between ACE level and disease chronicity based on patients’ HRCTs is statistically significant ($p$-value=0.045); ** There was no statistically significant difference between typical-atypical HRCT presentations categorized based on patients’ ACE level ($p$-value=0.145).
Conclusions

In this study, we demonstrated that chronicity of sarcoidosis according to patients’ HRCT presentations is inversely related to their ACE levels. This is considered another diagnostic clue in patients whose ACE levels and pathologic analyses are inconclusive.

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