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RESEARCH ARTICLE / ÖZGÜN ARAŞTIRMA

Evaluation of the Relationship between Clinical-Radiological Findings and Serum Angiotensin Converting Enzyme Levels in Sarcoidosis

Sarkoidozda Klinik-Radyolojik Bulgular ile Serum Anjiyotensin Dönüştürücü Enzim Düzeyi İlişkisinin Değerlendirilmesi

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ABSTRACT

Objective: Although it is known that angiotensin converting enzyme (ACE) levels, which are used in the diagnosis of sarcoidosis as a biomarker, show disease activity and granuloma load, they do not progress high in all patients with an active disease. Our study aimed to present the clinical and radiological differences between sarcoidosis patients with normal ACE levels and those with high ACE levels.

Material and Methods: The study was carried out by retrospectively examining the clinical and radiological data of patients who were monitored diagnosis of sarcoidosis at our unit between January 2013 and June 2020. The patients were divided into two groups as the normal ACE group and high ACE group based on their ACE levels. These two groups were compared in terms of age, sex, symptoms, presence of comorbidities, smoking status, and presence of extrapulmonary involvement. By examining the computerized thorax tomography images of both groups, comparisons were made based on lymph nodes and parenchymal lesions, as well as disease stages. The information on sex, age, symptoms, existing comorbidities and extrapulmonary involvement regions was assessed.

Results: The mean age of female patients was 54.17±13.30 years, while the mean age of male patients was 46.62±15.72 years, and the difference was statistically significant. p=0.016). No significant difference was observed between the normal ACE group and the high ACE group in terms of age, sex, symptoms on admission, comorbid diseases, and smoking status. There was no statistically significant difference between the groups in terms of numbers of extrapulmonary involvement. The conglomerated lymph nodes were significantly higher in the high ACE group (p=0.023). When the ACE levels were compared to the number of lobes in the lung where nodules were detected (p=0.026), minimum and maximum diameters of lymph nodes (respectively, p=0.038 and 0.021) and intrathoracic and extrathoracic total involved lymph node station numbers (p=0.003), positive relation was observed.

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Conclusion: Our study showed that the ACE levels were higher in the sarcoidosis patients with larger, conglomerated, and more abundant lymph node and nodular lesions.

Keywords: Angiotensin converting enzyme, extrapulmonary involvement, lymph node, sarcoidosis.

ÖZ

Amaç: Sarkoidoz tanısında biyobelirteç olarak kullanılan anjiyotensin dönüştürücü enzim (ACE) düzeyinin hastalığın aktivitesini ve granülom yükünü gösterdiği bilinse de aktif hastalığı olan tüm hastalarda yüksek seyretmemektedir. Çalışmada, normal ACE düzeyine sahip sarkoidozlu hastalar ile yüksek düzeye sahip sarkoidozlu hastalar arasındaki klinik ve radyolojik farkları ortaya koymak amaçlandı.

Gereç ve Yöntemler: Çalışmada, Ocak 2013-Haziran 2020 tarihleri arasında sarkoidoz tanısı konularak takip ya da tedavi edilen hastaların klinik ve radyolojik verileri retrospektif olarak incelendi. Hastalar ACE düzeylerine göre normal ACE grubu ve yüksek ACE grubu olarak ikiye ayrıldı. Bu iki grup yaş, cinsiyet, semptomlar, komorbidite varlığı, sigara içim özellikleri ve ekstrapulmoner tutulum varlığı açısından karşılaştırıldı. Her iki grubun bilgisayarlı toraks tomografi görüntüleri incelenerek lenf nodları ve parankimal lezyonlar ve hastalık evrelerine göre karşılaştırma yapıldı. Özellikler olarak cinsiyet, yaş, semptomlar, mevcut komorbiditeler ve ekstrapulmoner tutulum bölgeleri değerlendirildi.

Bulgular: Yaş ortalamaları kadın hastalarda 54,17±13,30, erkeklerde 46,62±15,72 idi, aralarındaki fark istatistiksel olarak anlamlıydı (p=0,016). Normal ACE grubu ile yüksek ACE grubu arasında yaş, cinsiyet, başvuru semptomları, komorbit hastalıklar ve sigara içme özellikleri açısından anlamlı farklılık gözlenmedi. Konglomere lenf nodları yüksek ACE grubunda anlamlı olarak daha fazlaydı (p=0,023). Akciğerde nodül saptanan lop sayısı (p=0,026), lenf nodlarının minimum ve maksimum çapı (sırasıyla p=0,038, 0,021), toraks içi ve dışı toplam tutulan lenf nodu istasyon sayısı (p=0,003) ile ACE düzeyleri karşılaştırıldığında ise istatistiksel olarak anlamlı düzeyde pozitif yönde bir ilişki saptandı.

Sonuç: Çalışmamız daha büyük, konglomere yerleşimli ve daha çok sayıda lenf nodu ve nodüler lezyonları olan sarkoidoz hastalarında ACE seviyelerinin daha yüksek seyrettiğini gösterdi.

Anahtar kelimeler: Anjiyotensin dönüştürücü enzim, ekstrapulmoner tutulum, lenf nodu, sarkoidoz.

INTRODUCTION

Sarcoidosis is a multisystemic granulomatous disease whose etiology is unknown which mostly involves young adults. While it may involve all organs and systems in the body, it most frequently involves the lungs and mediastinal lymph nodes.[1,2] The diagnosis of sarcoidosis is based on showing non-caseating granulomatous lesions accompanied by compatible clinical and radiological findings. Its most frequently observed form is Stage-I sarcoidosis characterized by bilateral hilarlymphadenopathy. It is needed to make a differential diagnosis of sarcoidosis in comparison to diseases such as lymphoma, fungal infection, and tuberculosis where growth in the mediastinal lymph nodes and pathological granulomatous inflammatory reaction may be observed.[3,4] Serum biomarkers have a limited role in the diagnosis of sarcoidosis. The most well-known biomarker is angiotensin converting enzyme (ACE). ACE is a glycoprotein that converts Angiotensin I to Angiotensin II. It is produced by epithelioid cells inside granulomas. It is a helpful marker in the diagnosis of the disease, determination of its activity and monitoring of response to treatment.[5,6] However, it is known that ACE levels may also rise in diseases such as lymphoma, histoplasmosis, some connective tissue diseases, and tuberculosis.[7] In addition, ACE levels may be normal in some sarcoidosis cases. A study showed that the sensitivity of ACE was 41.4%, and its specificity was 89.9% for the diagnosis of sarcoidosis.[8] Although it is known that ACE levels show disease activity and granuloma load, there are insufficient data in the literature on why the ACE levels are normal in some patients with diffuse radiological findings and active symptoms. Knowing about the factor or factors creating this difference between patients with normal ACE levels and those with high ACE levels will increase the negative and positive predictive value of this marker which is very easy to measure in the diagnosis of the disease. In this study, it was aimed to investigate the clinical and radiological differences between sarcoidosis patients with normal ACE levels and those with high ACE levels and whether or not there is a negative or positive correlation between these assessment parameters and ACE levels.

MATERIAL AND METHODS

The study was carried out by retrospectively examining the clinical and radiological data of patients who were monitored or treated with the diagnosis of sarcoidosis at the Pulmonology Department of the Faculty of Medicine at Karadeniz Technical University between January 1, 2013, and June 1, 2020. The study was started after obtaining local ethics board approval. Patients whose computerized thorax tomography images at first presentation were unavailable in the system of our hospital were not included in the study.

The patients were divided into two groups based on their ACE levels. The group with the age ACE levels in the range of 8–52 U/L was called the normal ACE group, while the group with higher levels was called the high ACE group. These two groups were compared in terms of age, sex, symptoms, presence of comorbidities, smoking status, and presence of extrapulmonary involvement. In addition, by examining their computerized thorax tomography images, the two

Table 1: Demographic characteristics and symptoms of the patients

Demographic characteristics and symptoms	Total (n=101)		ACE-normal group (n=42)		ACE-high group (n=59)		p
	n	%	n	%	n	%	
Age (median [min-max])	51.00 (22–87)		50 (28–74)		53 (22–87)		0.25
Sex							
Female	72	71.3	27	64.3	45	76.3	0.18
Male	29	28.7	15	35.7	14	23.7	
Symptoms							
Cough	51	50.5	21	50	30	50.8	0.93
Phlegm	14	13.9	8	19	6	10.2	0.20
Dyspnea	45	44.6	18	42.9	27	45.8	0.77
Chest pain	12	11.9	3	7.1	9	15.3	0.35
Skin lesion	21	20.8	9	21.4	12	20.3	0.89
Arthralgia	19	18.8	7	16.7	12	20.3	0.64
Palpitations	1	1.0	0	0.0	1	1.7	0.39
Eye-related complaint	6	5.9	1	2.4	5	8.5	0.39
Asymptomatic	3	3.0	3	7.1	0	0.0	0.69
Comorbidity							
Comorbid disease	51	51	18	42.9	33	56.9	0.16
Asthma	9	8.9	5	11.9	4	6.8	0.48
COPD	1	1.0	1	2.4	0	0.0	0.23
DM	12	11.5	6	14.3	6	10.2	0.54
CTD	3	3.0	3	7.1	0	0.0	0.69
HT	26	25.7	9	21.4	17	28.8	0.40
Other	18	17.8	8	19	10	16.9	0.78
Smoking status							
Never	64	77.1	23	69.7	41	82	0.23
Active smoker	6	7.2	2	6.1	4	8.0	
Quit	13	15.7	8	24.2	5	10	
Smoking duration (packs/year) (median [min-max])	15 (3–45)		15 (3–45)		11.5 (5–40)		0.72

ACE: Angiotensin converting enzyme, COPD: Chronic obstructive pulmonary disease, DM: Diabetes mellitus, CTD: Connective tissue disease, HT: Hypertension, Min: Minimum, Max: Maximum.

groups were assessed in terms of the localization, size, density and homogeneity of mediastinal lymph nodes, presence of necrosis or calcification, numbers of intrathoracic and extrathoracic lymph nodes involved, and sarcoidosis stage based on PA AC radiography and thorax tomography. Parenchymal lesions were compared in terms of nodules, ground glass appearance, reticular opacity, presence of consolidation, macroscopic properties of nodules, and number of lobes with nodules. The Somatom (Siemens, Forchhim, Germany) device at our hospital was used for computerized thorax tomography. For EBUS imaging and sampling, an Olympus EVIS EXERA II CV-180 device was used. Lymph node localization assessment was made based on Wang's lymph node map (2R, 2L, 4R, 4L, etc.). Lymphadenopathy density measurements were made based on the largest lymph node, and calculations were made based on Hounsfield units (HU) in a rectangular area contacting the LAP border from four corners in the tomography cross-section where lymphadenopathy showed a broad area in the axial plane. The maximum, minimum, and mean densities measured at the marked region were recorded. The measurements were made by the same person in all patients. As clinical characteristics, sex, age, symptoms, existing comorbidities, and extrapulmonary involvement regions were assessed. The correlation between the obtained numerical data and the ACE levels was assessed without separation into groups.

Table 2: Intergroup comparison based on extrapulmonary involvement regions

Extrapulmonary involvement regions	Total (n=101)		ACE-normal group (n=42)		ACE-high group (n=59)		p
	n	%	n	%	n	%	
Eye involvement	12	11.9	2	4.8	10	16.9	0.11
Skin involvement	16	15.8	6	14.3	10	16.9	0.71
CNS involvement	3	3.0	2	4.8	1	1.7	0.56
Joint involvement	4	4.0	0	0.0	4	6.8	0.13
Renal involvement	1	1.0	0	0.0	1	1.7	1.0
Liver involvement	1	1.0	1	2.4	0	0.0	0.41
Spleen involvement	5	5.0	1	2.4	4	6.8	0.39
Other	2	2.0	1	2.4	1	1.7	1.0

ACE: Angiotensin converting enzyme, CNS: Central nervous system.

Statistical Analysis

To test the normal distribution of the continuous variables, Kolmogorov-Smirnov test was used. The data characterized by a normal distribution are presented as mean±standard deviation. Student's t-test was used to compare the normally distributed data. Mann-Whitney U test was used to compare the non-normally distributed data. The discrete variables were compared by using Chi-squared test. P<0.05 was accepted as statistically significant. The data were analyzed using the SPSS statistical software (version 13.01, serial number 9069728, SPSS Inc., Chicago).

RESULTS

One hundred and two patients who were diagnosed with sarcoidosis within the specified dates whose file information, thorax tomography on admission, and if any, abdominal tomography images were available were included in the study. Among the patients, 72 (71.3%) were female, and 29 (28.7%) were male. The mean age was 54.17±13.30 years among the female patients and 46.62±15.72 years among the male patients, and the difference was significant (p=0.016). While the median ACE value of all patients was 60 (10.8–285.2), this was 61 (10.8–186.3) for the female patients and 50 (19–285.2) for the male patients. Without regard to the sexes, the ACE values of 42 patients (41.6%) were normal, while those of 59 (58.4%) were high. Based on the sexes, 14 of the male patients (48.3%) and 45 of the female patients (62.5%) had high ACE values. No significant difference was observed between the normal ACE group and the high ACE group in terms of age, sex, admission symptoms, comorbid diseases, or smoking characteristics (Table 1).

When the extrapulmonary involvement regions of the patients were examined, the most frequent involvement was skin involvement with 16 patients (15.8%), which was followed by eye involvement with 12 patients (11.9%). There was no significant difference between the normal ACE and high ACE groups in terms of the numbers of extrapulmonary involvements (Table 2).

When the two groups were compared based on their determined maximum and minimum LAP diameters, maximum, minimum, and mean LAP densities and intrathoracic and extrathoracic involved lymph node station numbers, no significant difference was determined (Table 3).

There was no significant difference between the high ACE and normal ACE groups in terms of the presence or absence of necrosis or calcification in the lymph nodes. Considering the localization forms of lymph nodes, while there was non-conglomerated localization in 48 patients in the high ACE group (82.8%), 10 patients (17.2%) had conglomerated localization. In the normal ACE group, while there was non-conglomerated localization in 41 patients (97.6%), only 1 patient (2.4%) showed conglomeration, and this difference was statistically significant (p=0.023). As tomographic image parenchymal findings, presence and absence of reticulation, ground glass appearance, consolidation, and nodules were checked in both groups. Nodular lesions were assessed to be micronodules if under 1 cm and macronodules if over 1 cm. However, there was also no significant difference between the groups in terms of these characteristics (Table 4).

When the relation between the ACE levels of all patients and the obtained numerical parameters was assessed, no relation could be determined between the patient age, smoking duration, lymph node mean density, intrathoracic involved lymph node station number, and the ACE levels. The numbers of lobes in the lung with nodules and the ACE levels were significantly and positively correlated (p=0.026). There was also a significant and positive relation between the minimum and maximum diameters of lymph nodes and the ACE levels (respectively, p=0.038 and 0.021). When the intrathoracic and extrathoracic total involved lymph node station numbers and ACE levels were compared, a significant and positive relation was determined (p=0.003) (Table 5).

DISCUSSION

In sarcoidosis, which is a multisystemic granulomatous disease, the diagnosis is based on the clinic, radiology, and tissue biopsy.[9] The place of serum biomarkers in the diagnosis is highly limited. While ACE, which is the most well-known biomarker and known to be syn-

Table 3: Intergroup comparison based on lymph node characteristics

Lymph node characteristics	Normal ACE			High ACE			Total			p
	Median	Min	Max	Median	Min	Max	Median	Min	Max	
Maximum LAP diameter (mm)	24.5	7	42	26	10	51	26	7	51	0.16
Minimum LAP diameter (mm)	18	7	30	19	6	30	18	6	30	0.27
Minimum LAP density (HU)	–2	–56	40	–1	–67	50	–1	–67	50	0.72
Maximum LAP density (HU)	97	37	163	96	42	368	96	37	368	0.48
Mean LAP density (HU)	49.8	–6.5	89.1	51.2	14.5	91.9	50.69	–6.5	91.9	0.31
Total involved stations	6	2	9	6	1	22	6	1	22	0.50
Intrathoracic LAP stations	6	2	8	8	0	8	6	0	8	0.58

ACE: Angiotensin converting enzyme, LAP: Lymphadenopathy, Min: Minimum, Max: Maximum.

Table 4: Intergroup comparison based on lymph node and parenchyma characteristics

Lymph node and parenchyma characteristics	Total (n=101)		ACE-normal group (n=42)		ACE-high group (n=59)		p
	n	%	n	%	n	%	
Lymph node localization form							
Non-conglomerated	89	89.0	41	97.6	48	82.8	0.023
Conglomerated	11	11	1	2.4	10	17.2	
Lymph node homogeneity	79	78.2	31	73.8	48	81.4	0.36
Lymph node necrosis	9	8.9	6	14.3	3	5.1	0.15
Lymph node calcification	12	11.9	6	14.3	6	10.2	0.54
Parenchymal findings							
Reticulation	10	9.9	5	11.9	5	8.5	0.73
Ground flass	25	24.8	11	26.2	14	23.7	0.77
Consolidation	16	15.8	8	19	8	13.6	0.45
Nodule	65	64.4	25	59.5	40	67.8	0.39
Nodule property							
Micronodule	45	69.2	18	72	27	67.5	0.80
Macronodule	13	20	4	16	9	22.5	
Both	7	10.8	3	12	4	10	
Disease stage							
Stage I	18	17.8	9	21.4	9	15.3	0.34
Stage II	82	81.2	32	76.2	50	84.7	
Stage III	1	1.0	1	2.4	0	0.0	

ACE: Angiotensin converting enzyme.

thesized from granuloma structures, had a high specificity (89.9%) for sarcoidosis, it has a low sensitivity (41.43%).[8] This situation is explained as that ACE levels are related to disease activity. However, the ACE levels in patients with active symptoms and findings may also be found low, and there are not enough data in the literature on the reason for this. In our study, we aimed to determine whether or not there were clinical and radiological differences between those with normal ACE levels and those with high ACE levels among patients with a diagnosis of sarcoidosis who had active symptoms and findings. We observed that there was no significant difference between the groups in terms of their mean age, sex, admission symptoms, comorbid diseases, and smoking history. In similarity to our study, in

Table 5: Relation between ACE levels and demographic and radiological data

Demographic and radiological data	Relation with ACE Levels	
	R	p
Age	–0.094	0.34
Smoking duration (packs/year)	–0.238	0.34
Maximum LAP diameter (mm)	0.229	**0.021**
Minimum LAP diameter (mm)	0.207	**0.038**
Mean LAP density	0.077	0.44
Number of intrathoracic stations with LAP	0.106	0.29
Total number of stations with LAP	0.295	**0.003**
Total number of lobes with nodules	0.277	**0.026**
Disease stage	0.156	0.11

ACE: Angiotensin converting enzyme, LAP: Lymphadenopathy

a study where sarcoidosis patients with normal ACE levels and those with high ACE levels were compared, no difference could be found in terms of age and sex. In their study, the most frequently encountered extrathoracic involvement was arthritis. Lung radiographies were assessed only based on the presence and absence of LAP, and no difference was found between the two groups. In difference to our study, their study compared the ionized calcium values of the two groups, and these were found to be significantly higher in the high ACE group.[10] In the study by Yasar et al.[11] which investigated the diagnostic value of ACE levels in detection of extrathoracic involvement in sarcoidosis, the ACE levels in the pulmonary sarcoidosis group with extrapulmonary involvement were found to be significantly higher than those in the group with only pulmonary involvement. In a similar study conducted by Lebedeva et al.,[12] while the ACE level in pulmonary sarcoidosis patients with extrathoracic involvement was 63.7 (49.1–79.8) μg/L, this value in the pulmonary sarcoidosis patient group without active extrapulmonary involvement regions was 43.1 (32.5–47.2) μg/L, and the difference was statistically significant. In our study, when the extrapulmonary involvement regions were examined, it was seen that the most frequent involvement was skin involvement among all patients, and there was no significant difference between the two groups. In the comparison of the radiological characteristics of the patients, there was no significant difference between the two groups in terms of their lymph node diameters, densities, and involved stations, but in terms of their lymph node localizations, it was observed that the rates of non-conglomerated localization were significantly higher in the normal ACE group, whereas the rates of conglomerated localization were significantly higher in the high ACE group (p=0.023).

In the study conducted by Lieberman on patients diagnosed with sarcoidosis, when ACE levels were compared based on disease stages, it was observed that the levels were higher in Stage II disease. While this difference was significant between the groups with Stage I and Stage II disease, it was not significant between the groups with Stage II and Stage III disease.[13] In our study, no significant difference was observed between the two groups in terms of the disease stages. The two groups also showed similar results in terms of the parenchymal findings of sarcoidosis.

When we looked at the correlations between non-categorical parameters obtained from the study data among all patients and the ACE levels, we found no correlation between the age, smoking duration, lymph node mean density, intrapulmonary involved lymph node station numbers, and the ACE levels. Nevertheless, there was a significant and positive correlation between the ACE levels and the minimum and maximum diameters of lymph nodes, total number of involved lymph node stations in the body, and number of lung lobes showing nodules.

Our study showed that the ACE levels in the sarcoidosis patients with larger, conglomerated and more abundant lymph nodes and nodular lesions were higher, and this result supported the correlation between disease activity and ACE levels. However, our data fell short in explaining how the ACE levels in the patients with several active symptoms and radiological findings could stay normal. The small sample size and the retrospective nature of the study could have played a role in this limitation. We believe investigating this issue with a broader patient population and additional parameters may provide useful results.

Disclosures

Ethics Committee Approval: The study was approved by The Karadeniz Technical University Faculty of Medicine Scientific Research Ethics Committe (date: 19.06.2020, number: 24237859-54).

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REFERENCES

1. Ungprasert P, Ryu JH, Matteson EL. Clinical manifestations, diagnosis, and treatment of sarcoidosis. Mayo Clin Proc Innov Qual Outcomes 2019;3:358–75.
2. Llanos O, Hamzeh N. Sarcoidosis. Med Clin North Am 2019;103:527–34.
3. Govender P, Berman JS. The diagnosis of sarcoidosis. Clin Chest Med 2015;36:585–602.
4. O'Regan A, Berman J. Sarcoidosis. Ann Int Med 2012;156:ITC5-1–15.
5. Ramachandraiah V, Aronow W, Chandy D. Pulmonary sarcoidosis: An update. Postgrad Med 2017;129:149–58.
6. Studdy PR, Bird R. Serum angiotensin converting enzyme in sarcoidosis--its value in present clinical practice. Ann Clin Biochem 1989;26:13–8.
7. Kraaijvanger R, Janssen Bonás M, Vorselaars ADM, Veltkamp M. Biomarkers in the diagnosis and prognosis of sarcoidosis: Current use and future prospects. Front Immunol 2020;11:1443.
8. Ungprasert P, Carmona EM, Crowson CS, Matteson EL. Diagnostic utility of angiotensin-converting enzyme in sarcoidosis: A population-based study. Lung 2016;194:91–5.
9. Spagnolo P, Rossi G, Trisolini R, Sverzellati N, Baughman RP, Wells AU.

Pulmonary sarcoidosis. Lancet Respir Med 2018;6:389–402.

10. Sejdic A, Graudal N, Baslund B. Clinical and biochemical presentation of sarcoidosis with high and normal serum angiotensin-converting enzyme. Scand J Rheumatol 2018;47:487–90.
11. Yasar Z, Özgül MA, Cetinkaya E, Kargi A, Gül Ş, Talay F, et al. Angiotensin-converting enzyme as a predictor of extrathoracic involvement of sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2016;32:318–24.
12. Lebedeva M, Popova E, Ponomarev A, Sergei B. Serum angiotensin converting enzyme (ACE) as additional clinical markers of activity of pulmonary and extra-pulmonary locations of sarcoidosis. Eur Respir J 2011;38:3734.
13. Lieberman J. The specificity and nature of serum-angiotensin-converting enzyme (serum ACE) elevations in sarcoidosis. Ann N Y Acad Sci 1976;278:488–97.