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ORIGINAL ARTICLE

Distribution of Activation Markers According to Stages in the Follow-Up of Patients with Sarcoidosis

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Abstract

Introduction: Sarcoidosis is a multisystem granulomatous disease known for its varied clinical presentation and diagnostic complexity. Despite advances in diagnostic modalities, sarcoidosis diagnosis remains challenging, particularly in asymptomatic cases. This study aimed to investigate the distribution and clinical implications of activation markers in sarcoidosis patients during different stages of follow-up.

Methods: A retrospective analysis was conducted on 61 sarcoidosis patients seen at a tertiary reference chest diseases hospital. Patient demographics, biochemical markers, respiratory function tests, and diagnostic procedures were evaluated. The CD4/CD8 ratio in bronchoalveolar lavage fluid, FEV1 percentage, DLCO (carbon monoxide diffusion test) levels, and serum ACE (serum angiotensin-converting enzyme), calcium were assessed at baseline and during follow-up visits.

Results: Analysis revealed significant variability in activation markers across different stages of sarcoidosis. Bronchoalveolar lavage fluid analysis showed elevated CD4/CD8 ratios (>3.5) in the majority of patients, indicative of disease activity. Additionally, FEV1 percentage and DLCO levels exhibited a progressive decline with advancing disease stages. Serum ACE and calcium levels varied inconsistently and did not show a significant correlation with disease activity.

Discussion and Conclusion: Assessment of activation markers, particularly the CD4/CD8 ratio in bronchoalveolar lavage fluid, provides valuable insights into disease activity and progression in sarcoidosis patients. Monitoring these markers during follow-up visits may aid in the early detection of disease exacerbations and guide treatment decisions. Further research is warranted to elucidate the clinical utility of these markers in sarcoidosis management.

Keywords: CD4/CD8 ratio; DLCO; sarcoidosis; serum ACE; serum calcium.

Sarcoidosis is a granulomatous disease, often an asymptomatic multisystem disorder that causes pulmonary and extrapulmonary involvement (eye, skin, heart, liver, peripheral lymph nodes, salivary glands, nervous system, musculoskeletal system) of unknown cause, frequently seen in young adults[1,2]. While the presence of typical clinical signs and symptoms contributes to rapid diagnosis, asymptomatic progression can cause a delay in diagnosis[1].

Sarcoidosis, a systemic inflammatory disease of unknown etiology that can affect almost every organ in the body, has symptoms and prognosis that depend not

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only on organ involvement but also on the patient's demographic characteristics and comorbidities[3]. The diagnosis of the disease is made based on a compatible clinical-radiological presentation, spirometry, serum ACE (angiotensin-converting enzyme), calcium, DLCO (carbon monoxide diffusion test), and histological evidence of non-caseating granulomas, as well as the exclusion of other granulomatous diseases[4].

In patients with suspected or diagnosed sarcoidosis, histopathological confirmation of the disease should be performed, the prevalence and severity of organ involvement should be assessed, the degree of disease activation should be investigated, and it should be determined whether the patient may benefit from treatment. Inflammatory markers play an important role in the diagnosis, assessment of disease activation, and follow-up of the disease[4]. In our study, we aimed to investigate the distribution and course of activation markers according to disease stages in the follow-up of patients with sarcoidosis.

Materials and Methods

Our study included 61 patients with sarcoidosis who were followed up with a diagnosis of sarcoidosis at a tertiary reference chest diseases hospital between December 2006 and December 2009. The demographic characteristics of the cases, biochemistry results, respiratory function tests, diagnostic methods, chest radiography, whether they received treatment or not, and any recurrences of their disease from the beginning of their disease to the present were recorded.

The cases were radiologically grouped as Stages 0, I, II, and III according to PA (posterior-anterior) chest radiography. At the sixth- and 12th-month follow-ups of the patients, the changes in ACE, calcium (Ca), FEV1, FEV1%, FEV1/FVC, and DLCO values were recorded according to the stages during the follow-up periods.

Statistical Analysis

While evaluating the findings obtained in the study, SPSS (Statistical Package for Social Sciences) for Windows 21.0 program was used for statistical analysis. Since this was a retrospective study, no sample size calculation was performed before the study commenced. Power analysis was conducted, and the power of the study was found to be 82%.

In the evaluation of study data, in addition to descriptive statistical methods (frequency, percentage, mean, standard deviation), the Kruskal-Wallis test was used to compare non-normally distributed parameters between more than two groups, and the Mann-Whitney U test was used to determine the group causing the difference. The results were evaluated at a 95% confidence interval, and the significance level was set at $p<0.05$.

Results

In our study, a total of 61 patients (mean age 35.01±0.12), including 14 (23%) males and 47 (77%) females, were examined. Fiberoptic bronchoscopy was conducted in 47 (77%) patients. Diagnoses were made using transbronchial needle aspiration in 20 cases, forceps biopsy in one case of endobronchial sarcoidosis, and lymph node biopsy with endobronchial ultrasound in another case. In the remaining 25 patients who underwent fiberoptic bronchoscopy, only BAL was performed. Bronchoscopic intervention was diagnostic in 35 (74.4%) of the cases in which fiberoptic bronchoscopy was performed. However, the procedure yielded no diagnosis in 12 patients. Among all patients, only one had evidence of endobronchial sarcoidosis.

In 12 of 44 patients who underwent BAL, the CD4/CD8 ratio was <3.5 and was not diagnostic. However, in 31 (70.45%) patients, the CD4/CD8 ratio in BAL was ≥3.5 (mean 6.9; max 16.4; min 3.5) and was considered diagnostic.

The diagnosis was made histopathologically by skin biopsy in two patients and by palpable cervical lymph node biopsy in three patients. Mediastinoscopic lymph node biopsy was performed for diagnosis in 16 (26.2%) cases. Extrapulmonary involvement was present in 10% of cases (two parotid, one spleen, and three skin findings).

The average serum ACE level was 70 µg/L (min 12; max 206 µg/L). Serum Ca^{+2} levels averaged 9 mg/dL (max 10.2; min 8.5 mg/dL). The mean values in respiratory function tests before treatment and follow-up were as follows: FEV1 2.25 L (77%); DLCO 87.4%.

The initial radiological stages of the patients were as follows: 35 patients were Stage I, 22 patients were Stage II, and four patients were Stage III. Steroid treatment was initiated in 11 (18.0%) patients for various indications. Respiratory function test levels according to the initial stage are presented in Table 1.

The changes in ACE, calcium, FEV1, FEV1%, FEV1/FVC, and DLCO values of the patients according to their stages at the sixth- and 12^{th}-month follow-up periods are presented in the tables.

- The FEV1% value in Stage I was found to be higher than in Stage III ($p=0.017$).

Table 1. Respiratory function testlevels of Sarkoidosis cases according to their initial stage

	Stage 1 (n=34)			Stage2(n=22)			Stage3(n=5)			p
	Median	Min.	Max.	Median	Min.	Max.	Median	Min.	Max.	
ACE	60.00	12.00	196.00	79.00	26.00	206.00	61.00	36.00	137.00	0.133**
Ca	9.20	8.60	10.20	9.30	8.60	10.20	9.00	8.50	9.10	0.276**
FEV1	2.44	0.87	3.94	2.19	1.11	3.63	1.87	0.96	2.50	0.087**
FEV1%	78.50	47.00	116.00	76.00	35.00	102.00	65.00	34.00	73.00	**0.044***
FEV1/FVC	83.00	62.00	111.00	83.00	61.00	90.20	83.00	76.00	126.00	0.965**
DLCO	87.50	65.00	130.00	79.00	49.00	119.00	71.00	62.00	90.00	**0.006***

ACE: Angiotensin Converting Enzyme; Ca: Calcium; FEV1: Force expiratory volume in 1 second; FEV1/FVC: Force expiratory volume in 1 second/Force vital capacity; DLCO: carbon monoxide diffusion test; *p<0.05 statistically significant Mann Whitney U test** Kruskal Wallis test.

- The DLCO value in Stage I was found to be higher than in Stage II (p=0.017) and Stage III (p=0.009) (Table 1).
- A statistically significant difference was found between ACE values according to stages. The Mann-Whitney U test was conducted to determine the stages responsible for this variation. The ACE value in Stage I was found to be lower than in Stage II (p=0.011). Serum ACE and PFT results of staged cases at the 12th month were analyzed *(when there was a patient in Stage III, the evaluation was made based on Stages I and II)* (Table 2).
- A statistically significant difference was found in calcium values according to the stages. The calcium value in Stage I was lower than in Stage II.

At the end of the sixth month of treatment or follow-up, a decrease in disease stage was detected in two patients. By the end of the 12th month, eight patients had a decrease in stage (Table 3).

No statistically significant difference was found between the 0th and 6th months (p>0.05) (Table 4).

No statistically significant difference was detected in DLCO values between the 0th and 12th months (p>0.05) (Table 5).

When analyzing the groups responsible for this difference, it was noted that the proportion of individuals with a decrease in DLCO stage was higher than those whose stage remained unchanged (p=0.006) (Table 6).

Table 2. 6th month serum ACE and PFT results of Sarcoidosis cases

	Stage1(n=35)			Stage2(n=22)			Stage3(n=4)			p
	Median	Min.	Max.	Median	Min.	Max.	Median	Min.	Max.	
ACE	44.00	10.00	143.00	65.00	20.00	143.00	69.00	34.00	120.00	**0.018***
Ca	9.20	8.90	10.40	9.25	8.70	10.30	9.00	8.20	9.80	0.319**
FEV1	2.38	0.86	3.81	2.16	1.32	3.62	1.58	0.78	2.57	0.096**
FEV1%	80.00	52.00	128.00	81.80	57.00	103.00	65.00	40.00	78.00	0.136**
FEV1/FVC	84.80	60.00	109.00	84.50	60.50	110.00	81.50	81.00	94,00	0.97**
DLCO	95.00	65.00	120.00	87.00	52.00	115.00	78.00	65.00	97.00	0.087**

ACE: Angiotensin Converting Enzyme; Ca: Calcium; FEV1: Force expiratory volume in 1 second; FEV1/FVC: Force expiratory volume in 1 second/Force vital capacity; DLCO: Carbon monoxide diffusion test; *p<0.05 statistically significant Mann Whitney U test **Kruskal Wallis test.

Table. 3 12-month serum ACE and PFT results of Sarcoidosis case

	Stage1 (n=39)			Stage2 (n=22)			p
	Median	Min.	Max.	Median	Min.	Max.	
ACE	30.00	9.00	142.00	30.00	14.00	91.00	0.253
CA	9.00	8.00	10.60	9.30	8.50	10.20	**0.049**
FEV1	2.49	1.02	3.55	2.20	0.83	3.63	0.11
FEV1%	84.00	45.00	130,00	78.00	31.00	92.00	0.071
FEV1/FVC	83.00	59.00	110.00	83.80	65.00	92.60	0.869
DLCO	90.00	69.00	129.00	68.00	60.00	106.00	0.148

ACE: Angiotensin Converting Enzyme; Ca: calcium; FEV1: Force expiratory volume in 1 second; FEV1/FVC: Force expiratory volume in 1 second/force vital capacity; DLCO: Carbon monoxide diffusion test, p<0.05 statistically significant Mann Whitney U test.

Table 4. Stage change in sarcoidosis cases after 6 months of follow-up

	Degresse (n=2)	Stable (n=59)	P
ACE	-16.5±19	18.2±29	0.903
Ca	0.05±0.07	0.01±0.42	0.655
FEV1	0.58±0.50	0.02±0.36	0.068
FEV1%	8±4.24	2.48±11.02	0.138
FEV1/FVC	-0.65±3.74	0.30±10.9	0.715
DLCO	17±0	1.89±10.9	0.056

ACE: Angiotensin Converting Enzyme; Ca: calcium; FEV1: Force expiratory volume in 1 second; FEV1/FVC: Force expiratory volume in 1second/force vital capacity; DLCO: Carbon monoxide diffusion test; p<0.05 statistically significant Mann Whitney U test.

Table 5. Stage change in sarcoidosis cases after 6-12 months of follow-up

	Decrease (n=6)	Stable (n=55)	p
ACE	-34.3±32.5	-14.8±28.4	0.112
Ca	-0.15±0.56	-0.09±0.46	0.380
FEV1	0.05±0.18	0.09±0.28	0.971
FEV1%	-2.16±5.03	0.75±12.2	0.314
FEV1/FVC	-0.36±6.35	-0.17±9.63	0.875
DLCO	6.5±11.4	2.01±11.8	0.314

ACE; Angiotensin Converting Enzyme; Ca: calcium; FEV1: Force expiratory volume in 1 second); FEV1/FVC: Force expiratory volume in 1 second/force vital capacity; DLCO: Carbon monoxide diffusion test, p<0.05 statistically significant Mann Whitney U test.

Table 6. Stage change in Sarcoidosis cases after 0-12 months of follow-up

	Decrease (n=8)	Stable (n=53)	P
ACE	-51.2±40.5	-32.5±35.9	0.211
Ca	-0.1±0.56	-0.09±0.51	0.629
FEV1	0.30±0.47	0.11±0.33	0.417
FEV1%	7.37±13.2	2.4±13.1	0.586
FEV1/FVC	-3.65±17.3	0.63±10.2	0.915
DLCO	15.8±9.5	3.18±14.3	**0.006**

ACE: Angiotensin Converting Enzyme; Ca: calcium; FEV1: Force expiratory volume in 1 second; FEV1/FVC: Force expiratory volume in 1 second/force vital capacity; DLCO: Carbon monoxide diffusion test; p<0.05 statistically significant Mann Whitney U test.

Discussion

As the progression of sarcoidosis following diagnosis remains uncertain, determining the activity status of patients and predicting those who may advance to fibrosis, leading to respiratory function decline, is challenging. Sarcoidosis activity involves ongoing clinical, radiological, and physiological alterations. This multisystem condition plays a crucial role in treatment decisions for affected organs under clinical surveillance, influencing both the type and duration of treatment.

Despite being classified as a disease of unknown etiology, various factors are implicated in the development of sarcoidosis. While some studies indicate that the disease prevalence is at least twice as high in females, others suggest a slightly elevated frequency[5]. Studies conducted in Türkiye have also shown that the disease is more common in women, consistent with our findings[6]. In our series, the disease was most frequently observed in the third and fourth decades of life. Sarcoidosis, which predominantly occurs between the ages of 20 and 40, is seen in only 2% of individuals under the age of 10 and in 4% of those over the age of 60[7].

When cases in our study were evaluated according to radiological stage, the initial stages were as follows: 35 patients were Stage I, 22 were Stage II, and 4 were Stage III. The higher number of cases in Stage I and Stage II aligns with findings from other studies conducted in Türkiye[8,9].

The diagnostic bronchoscopic procedures performed in sarcoidosis include EBB (endobronchial biopsy) as well as TBB (transbronchial biopsy). In Stage I and II cases, the diagnostic yield of bronchoscopy increases with the addition of transbronchial needle aspiration biopsy[10]. Various retrospective studies have reported the diagnostic yield of EBB to range between 41% and 71%[11-13]. In our series, fiberoptic bronchoscopy was performed in 47 (77%) of the patients, with a diagnostic yield of 35 (74.4%).

ACE levels, which serve as a determinant for disease activity and monitoring in sarcoidosis, are elevated in 30-80% of patients[14]. A study conducted in Türkiye found an ACE elevation rate of 61%[15]. In our study, serum ACE levels were measured in all patients, with an average value of 70.6. Despite numerous studies indicating elevated serum ACE levels in active cases, we did not observe a significant difference in serum ACE levels between active and inactive sarcoidosis cases, consistent with findings from other studies[16,17]. Similar to our results, previous studies have not shown a significant relationship between radiological stage and serum ACE levels.

If the BAL (bronchoalveolar lavage) CD4/CD8 ratio is >3.5 or 4, sensitivity has been reported as 52-59% and specificity as 94-96%. In patients clinically compatible with sarcoidosis, an increased CD4/CD8 ratio in BAL may support the diagnosis and eliminate the need for biopsy[18]. Kantrow et al.[19] reported that BAL lymphocytosis is not a universal finding in sarcoidosis, with BAL lymphocyte levels <16% in one-third of biopsy-confirmed cases and a CD4/CD8 ratio >4 in 40% of cases.

A study demonstrated that the BAL lymphocyte ratio was lower in Stage III cases compared to Stages I and II. It also

showed a negative correlation between the CD4/CD8 ratio and radiological stage, with the highest levels observed in Stage I cases. In our study, the CD4/CD8 ratio was <3.5 in 12 of 44 patients who underwent BAL, which was not diagnostic[20]. However, in 31 (70.45%) patients, the CD4/CD8 ratio in BAL was ≥3.5 (mean 6.9; max 16.4; min 3.5) and was considered diagnostic.

The most common functional disorder in sarcoidosis is the restrictive type disorder. Restrictive-type respiratory disorder has been reported in 6% of newly diagnosed patients with sarcoidosis[21]. As sarcoidosis progresses from Stage I to Stage IV, declines in respiratory function tests become more pronounced, with restrictive-type disorders being particularly notable[21,22]. Some studies have shown that granuloma density is inversely proportional to FEV1 and FVC[23]. In the presence of severe infiltration and distortion on chest radiography (Stages III and IV), reductions in FEV1 and lung volumes, hypoxemia, impaired diffusion capacity (DLCO), and decreased exercise capacity are observed[24,25].

On the other hand, pulmonary function tests may remain normal even when parenchymal involvement is evident on PA chest radiography[14]. In a study conducted in Türkiye, a restrictive pattern was reported at a rate of 13%, an obstructive pattern at 7%, and a combined respiratory disorder at 4%[26]. Similarly, in a study involving 107 newly diagnosed sarcoidosis cases, airway obstruction was reported in 57% of cases, while a restrictive defect was observed in 6%[21].

In our study, we found that FEV1/FVC remained consistent across different stages during the initial evaluation. However, there was a statistically significant decline in FEV1% values in advanced stages (p=0.044), indicating worsening respiratory function. Similarly, DLCO results showed a decrease with increasing stage (p=0.006). Although no statistically significant difference was found in the follow-up parameters in the first six months, by the end of the first year, a statistically significant difference was observed in DLCO values when follow-up parameters were compared with baseline values (p<0.05). When analyzing the groups responsible for this difference, it was found that DLCO was higher in those whose stage decreased than in those whose stage remained unchanged (p=0.013).

Long-term follow-up studies have demonstrated a correlation between the severity of parenchymal lesions and impairments in respiratory function[4]. While respiratory function test impairment is observed in 20% of patients with Stage I sarcoidosis, this rate increases to 40-70% in Stages II, III, and IV[1]. Many studies have shown an increasing prevalence of low DLCO with advancing radiological stage. In sarcoidosis, a decrease in the alveolar-capillary bed, thickening of the alveolar-capillary membrane, and a reduction in pulmonary capillary blood volume contribute to the decline in diffusion capacity. Impaired diffusion has both a membrane and a blood component, with studies indicating that the membrane component is more significant in interstitial lung diseases. It has been shown that the reduction in the average alveolar surface within the membrane component plays a more significant role than the increase in membrane thickness. While DLCO decreases in many patients, the fact that the DLCO/VA ratio remains normal or close to normal supports this observation[14]. In patients with normal chest radiography and no symptoms, a 25-50% decrease in DLCO may be observed even when other respiratory function tests are normal[1,27].

Conclusion

In our study, which investigated activation markers according to stages in patients with sarcoidosis, the CD4/CD8 ratio in BAL fluid above 3.5 at the time of diagnosis, FEV1 percentage, DLCO level, and the evaluation of ACE, serum calcium, and DLCO levels during follow-up may serve as valuable tools for clinicians, especially in cases where staging cannot be performed.

Ethics Committee Approval: It was done as a medical specialization thesis in 2009 at the department of Chest Dissease,Süreyyapaşa Cheast Diseases and Chest Surgery Traning and Research Hospital.

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