# Is Lymphopenia Detected in Sarcoidosis Associated with the Disease Activity?

- © Coşkun Doğan,¹ © Sevda Şener Cömert,¹ © Benan Çağlayan,²
- © Elif Torun Parmaksız,¹ © Nesrin Kıral,¹ © Recep Demirhan,³
- Ali Fidan, De Seda Beyhan Sağmen

'Department of Chest Diseases, Health Science University Kartal Dr. Lütfi Kırdar Training and Research Hospital, İstanbul, Turkey 'Department of Chest Diseases Koç University Faculty of Medicine, İstanbul, Turkey <sup>3</sup> Department of Thoracic Surgery, Health Science University Kartal Dr. Lütfi Kırdar Training and Research Hospital, İstanbul, Turkey

> Submitted: 13.12.2018 Accepted: 03.04.2019

Correspondence: Coşkun Doğan, Kartal Dr. Lütfi Kırdar Eğitim ve Araştırma Hastanesi, Göğüs Hastalıkları Kliniği, İstanbul, Turkey E-mail: coskund24@hotmail.com



**Keywords:** Diffusing capacity for carbon monoxide; lymphopenia; sarcoidosis.



This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License

#### **ABSTRACT**

**Objective:** The association of lymphopenia detected in patients with sarcoidosis with disease activity was investigated in the present study.

**Methods:** Patients who were diagnosed as having sarcoidosis and healthy volunteers/individuals with no diagnosis of active disease between July 2016 and June 2017 were included in this study. Patients who were detected to have an absolute lymphocyte count (ALC) of <1.3 × 10³/mm³ were accepted as lymphopenic patients. The detection rates of lymphopenia were compared between two groups. The respiratory function testing-diffusing capacity of the lungs for carbon monoxide (RFT-DLCO) levels and the high-resolution computed tomography (HRCT) results of patients with and without lymphopenia in the sarcoidosis group were compared.

**Results:** In the sarcoidosis group, 77 patients were included, and in the control group, 41 patients were included. The number of lymphopenic patients in the sarcoidosis group was 21 (27.2%), and that in the control group was 1 (2.4%) (p=0.001). The percentaged DLCO value of 33 patients (28%) was below 80%; however, the percentaged DLCO value of 44 patients was higher than 80% in the sarcoidosis group. The mean ALC of patients in the sarcoidosis group who had a DLCO value of <80% was  $1.6\pm0.7$ ; however, the mean ALC of patients who had a DLCO value of >80% was  $2\pm0.7$  (p=0.016). A positive correlation was detected between ALC and DLCO% (p=0.044, r=0.230). Although lymphopenia was detected in 42% of patients whose DLCO value was <80%, lymphopenia was detected in 15% of patients whose DLCO value was >80% (p=0.01). No significant association was detected among the sarcoidosis stage, symptom, and radiologic findings of the patients with the absolute lymphocyte count (p>0.05).

**Conclusion:** Lymphopenia is frequently detected in patients with sarcoidosis. Lower DLCO values may be detected in patients with lymphopenic sarcoidosis.

# **INTRODUCTION**

Sarcoidosis is a systemic granulomatous disease with non-calcified granuloma infiltration of the involved organ, the etiology of which is not known. Sarcoid granuloma consists of mononuclear phagocytes and epithelioid histiocytes at the center, and CD4 and CD8 T lymphocytes and B lymphocytes at the periphery. CD4 T lymphocytes induce and maintain the development of sarcoid granuloma. [1,2] Infiltration of the affected organs by lymphocytes is characteristic of sarcoidosis. In the early stages of sarcoidosis, CD4 T lymphocytes accumulate in all the diseased areas, alveolar cavities, and interstitium.

The rates of T-helper lymphocytes, active T lymphocytes, and CD4/CD8 lymphocyte ratio increase in the bron-

choalveolar lavage (BAL) fluid of the cases.<sup>[3,4]</sup> Because the lymphocytes are predominant cells involved in the etiopathogenesis, sarcoidosis is defined as an alveolitis initiated by lymphocyte accumulation.<sup>[5]</sup> Progressive radiological changes in lung sarcoidosis, more than 20% decrease in the DLCO test, and disturbing symptoms are indicators of active disease and indication for treatment.<sup>[1]</sup> One of the most common hematologic changes seen in sarcoidosis is lymphopenia.<sup>[6]</sup> Although sarcoidosis-associated lymphopenia is thought to be related to depletion of lymphocytes during the active period of the disease or to the accumulation of lymphocytes around granulomas, it may also be related to bone marrow involvement or chronic disease.<sup>[7,8]</sup>

The presence of lymphopenia in sarcoidosis has long been known and has been proven with scientific studies. [9-11]

152 South, Clin, Ist, Euras,

However, few studies have investigated the relationship between lymphopenia and disease activity in sarcoidosis. <sup>[12]</sup> In our study, the relationship between high-resolution computed tomography (HRCT) findings and pulmonary function test-carbon monoxide diffusion test (PFT-DLCO) values was investigated in patients with sarcoidosis.

#### **MATERIALS AND METHODS**

Our study was planned as a prospective/controlled cross-sectional trial in compliance with the international Helsinki Declaration between July 2016 and June 2017 and an approval from local ethics committee was obtained. Patients who were followed up with clinical, radiological, and histopathological diagnosis of sarcoidosis were enrolled as the sarcoidosis group in our outpatient clinic. Newly diagnosed cases with uncertain clinical, radiological, and histopathological diagnosis of sarcoidosis were not included in the study. During the same period, healthy volunteers who did not have active disease and those who were referred/presented to our outpatient clinic for the purpose of examination were evaluated as the control group. In both groups, cases with hematological disease, which may affect the lymphocyte count in peripheral blood counts, and those with a recent viral or bacterial infection were not included in the study. Patients receiving treatment (corticosteroids) were not included in the study because their lymphocyte count could have been altered. Absolute lymphocyte counts (ALCs) in peripheral blood were recorded both in the sarcoidosis and control groups. The normal range of ALCs was 1.3-2.0 × 10<sup>3</sup>/mm in our laboratory. Patients with ALCs <1.3 × 10<sup>3</sup>/mm<sup>3</sup> were considered lymphopenic. ALCs of both groups were compared. HRCT and RFT-DLCO values were recorded in the sarcoidosis group. DLCO values and HRCT findings of patients with and without lymphopenia in the sarcoidosis group were compared with each other.

# Pulmonary function test and carbon monoxide diffusion test

PFT-DLCO tests were performed according to the guidelines prepared for the standardization of pulmonary function tests by the American Thoracic Society and the European Respiratory Society.<sup>[13,14]</sup> The measurement of PFT and DLCO was performed with the 'single breath hold' technique using the Sensor Medics Vi-Max-22, Care Fusion (San Diego, California) device. Forced vital capacity (FVC), forced expiratory volume in one second (FEV<sub>1</sub>), and FEV<sub>1</sub>/FVC values were recorded in liters and percentages, and 80–120% of the expected values for each lung volume were considered to be normal values. DLCO (mL/min/mmHg/L) and DLCO/alveolar ventilation rate (VA) (DLCO/L, %) 80–120% of the expected value for each lung volume were considered to be normal values and recorded in liters and percentages.

## High-resolution pulmonary tomography (HRPT)

After deep inspiration, non-contrasted HRPT images of all cases were obtained at an axial plane starting from apex up to the end of the diaphragm using a Siemens Medical Solutions-2010 (Forchheim-Germany) device with the following settings: gantry movement of 15 mm/rot; tube potential of 120 kV/200 reference mAs, slice width of 2 mm, 512 × 512 pixel matrix and bone algorithm, window width of 1200 Hounsfield unit (HU), and window level of 700 HU.

#### Statistical analysis

Statistical analysis was performed using SPSS 17.0 (IBM Inc. Released 2008. SPSS Statistic for Windows Chicago, USA) program. In descriptive statistics, continuous variables were expressed as mean ± standard deviation and categorical variables as percentages. The Kolmogorov–Smirnov test was used for normal distribution tests. Data of the groups were evaluated using chi-square, t-test, and Mann–Whitney U tests. A Pearson correlation analysis was performed to evaluate the relationship between RFT-DLCO parameters and ALCs. The correlation coefficient was expressed as r. A p value of <0.05 was considered the level of statistical significance in all tests.

#### **RESULTS**

Seventeen (22.1%) male and sixty (77.9%) female patients with a mean age of  $48.1\pm14.4$  years were included in the sarcoidosis group. Seventeen (22.1%) male and twenty-four (58.5%) female patients with a mean age of  $40.6\pm12.2$  years were included in the control group.

The absolute lymphocyte count (ALC) was  $1.8\pm0.7 \times 10^3/\text{ml}$  in the sarcoidosis group and  $1.9\pm0.4 \times 10^3/\text{ml}$  in the control group (p=0.409). In the sarcoidosis group, 21 (27.2%) lymphopenic (ALC <1.3 ×  $10^3/\text{ml}$ ) cases were found and in the control group 1 (2.4%) lymphopenic patient was found (p=0.001) (Table 1).

 Table 1.
 Absolute lymphocyte counts in sarcoidosis and control groups

	ALC (mean±SD) (10³/mm)	Number (%) of the cases with ALCs <1.3 x 10 <sup>3</sup> /mm	Number (%) of the cases with ALCs >1.3 x 10 <sup>3</sup> /mm
Sarcoidosis group (n=77)	1.8±0.7	21 (27.2)	56 (72.8)
Control group (n=41)	1.9±0.4	I (2.4)	40 (97.6)
p-value	0.409	0.001	0.001

Stage	Number (%) of the cases with ALCs $< 1.3 \times 10^3 / ml$	Stage	Number (%) of the cases with ALCs $< 1.3 \times 10^3$ /ml	р
Stage 0	3 (15)	Stage I	9 (30)	0.317
Stage 0	3 (15)	Stage 2	7 (31.8)	0.284
Stage 0	3 (15)	Stage 3	3 (60)	0.252
Stage I	9 (30)	Stage 2	7 (31.8)	0.888
Stage I	9 (30)	Stage 3	2 (40)	0.640
Evre 2	7 (31.8)	Stage 3	2 (40)	0.571

Symptoms of the cases, and relationship between symptoms, and ALCs Number (%) of the cases with ALC <1.3 x 103/ml Symptoms Number (%) of the cases p Weakness (yes/no) 48 (62.3) / 29 (37.7) 13 (27) / 8 (27.5) 0.889 42 (54.5) / 35 (45.5) 11 (26.1) / 10 (28.5) Shortness of breath (yes/no) 0.815 32 (41.6) / 45 (58.4) 10 (31.2) / 11 (24.4) 0.509 Coughing (yes/no) Chest pain (yes/no) 23 (29.9) / 54 (70.1) 5 (21.7) / 16 (29.6) 0.477 0.270 Fever (yes/no) 10 (13) / 67 (87) 1 (10) / 20 (29.8) Weight loss (yes/no) 8 (10.4) / 69 (89.6) 2 (25) / 19 (27.5) 0.999 ALC: Absolute lymphocyte count.

**Table 4.** RFT-DLCO values of the cases in the sarcoidosis group

Mean±SD
76.8±7.4
2.53±0.7
91.2±17
3.15±0.9
98.7±17
6.61±2.4
83.4±18
1.99±1
101.4±16.9

RFT: Respiratory function testing; DLCO: Diffusing capacity of the lungs for carbon monoxide. FVC: Forced vital capacity; FEV1: Forced expiratory volume in one second; AV: Alveolar volume; SD: Standard deviation.

The sarcoidosis cases were in Stages 0 (n=20: 26%), I (n=30: 39%), 2 (n=22: 28.6%), and 3 (n=5: 6.5%). We did not have any case with Stage 4 sarcoidosis. No statistically significant relationship was detected between the stages of the cases and the ALCs (p>0.05) (Table 2).

The most frequently seen symptoms were weakness in 48 (62.3%) and, least frequently, weight loss in 8 (10.4%) patients. ALCs below  $1.3 \times 10^3/\text{ml}$  were detected in 13 (27%) of 48 (62.3%) patients with complaints of weakness and in 8 (27.5%) of 29 (37.7%) patients without fatigue. Any statistically significant relationship was not found between the patients with and without complaints of weakness (p=0.889). There was no statistically significant re-

lationship between ALCs and symptoms of the patients (p>0.05) (Table 3).

When the RFT results of the cases were examined, FVC values of 12 cases (15.5%) were lower than 80% in the sarcoidosis group, whereas FVC values of 65 (84.5%) cases were above 80%. Although 4 (33.3%) of the patients had FVC values below 80%, the number of ALCs were lower than  $1.3 \times 10^3/\text{ml}$  in 17 (26.1%) of the cases with FVC values above 80%. There was no statistically significant difference between the two groups (p=0.726). PFT-DLCO values of the cases are shown in Table 4, and the relationship between PFT-DLCO parameters and lymphopenia is presented in Table 5.

When DLCO test results of the cases were examined, DLCO% values of 33 cases (28%) in the sarcoidosis group were below 80%, whereas those of 44 (72%) cases were over 80%. A positive correlation was found between ALCs and DLCO% (p=0.044, r=0.230) (Fig. 1). The mean ALC of the patients with a DLCO value of <80% in the sarcoidosis group was  $1.6\pm0.7\times10^3$ /ml, whereas the mean ALC of the cases with a DLCO value of >80% was  $2\pm0.7\times10^3$ / ml (p=0.016). Leucopenia was present in 42.4% of the patients with a DLCO value of <80% and in 15.9% of patients with a DLCO value of <80% (p=0.01) (Table 5).

When HRCT findings of sarcoidosis cases were examined, the most common HRCT findings were the parenchymal nodules larger than 1 cm in 30 (38.9%) and hourglass appearance in 27 (35.1%) cases (Table 4). Parenchymal abnormality was detected in HRCT in 59 (76.7%) patients in the sarcoidosis group and it was not found in 18 (23.3%) cases. The mean ALC of the cases with parenchymal ab-

154 South. Clin. Ist. Euras.

Table 5.	Relationship	between	RFT-DLCO	parameters,	and lymphopenia
----------	--------------	---------	----------	-------------	-----------------

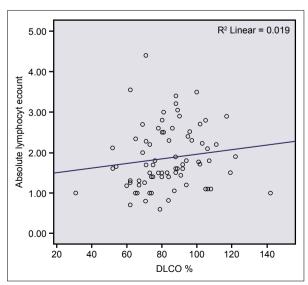
RFT-DLCO parameters	Number (%) of the cases	Number (%) of the cases with ALC $< 1.3 \times 10^3 / \text{ml}$	Number (%) of the cases with ALC $> 1.3 \times 10^3$ /ml	р	
FVC value <80%	12 (15.5)	4 (33.3)	8 (66.7)	0.726	
FVC value ≥80%	65 (84.5)	17 (26.1)	48 (73.9)		
FEVI value <80%	21 (27.2)	7 (33.3)	14 (66.7)	0.465	
FEVI value ≥80%	56 (72.8)	14 (25)	42 (75)		
DLCO value <80%	33 (28)	14 (42.4)	19 (57.6)	0.01	
DLCO value ≥80%	44 (72)	7 (15.9)	37 (84.1)		

RFT: Respiratory function testing; DLCO: Diffusing capacity of the lungs for carbon monoxide. FVC: Forced vital capacity. FEV1: Forced expiratory volume in one second. ALC: Absolute lymphocyte count.

 Table 6.
 HRCT findings of the cases and relationships between HRCT findings and ALCs

HRCT findings	Number (%) of the cases	Number (%) of the cases with ALC <1.3 x 10 <sup>3</sup> /ml	р	
Abnormal parenchymal sign (yes/no)	18 (24.6) / 59 (75.4)	5 (27.7) / 16 (27.1)	0.999	
Hilar-mediastinal LAP (yes/no)	57 (74) / 20 (26)	18 (31.5) / 3 (15)	0.152	
Parenchymal >1 cm nodule (yes/no)	30 (38.9) / 47 (61.1)	7 (23.3) / 14 (29.7)	0.535	
Hourglass sign (var/yok)	27 (35.1) / 50 (64.9)	7 (25.9) / 14 (28)	0.845	
Sequel band sign (yes/no)	22 (28.6) / 55 (71.4)	4 (18.1) / 17 (30.9)	0.257	
Bilateral ILSK (yes/no)	11 (14.2) / 66 (85.8)	5 (45.4) / 18 (27.2)	0.159	
Parenchymal I-2 mm nodules (yes/no)	10 (13) / 67 (87)	5 (50) / 16 (23.8)	0.125	
Reticular pattern (yes/no)	9 (11.6) / 68 (88.4)	2 (22.2) / 19 (27.9)	0.999	
Reticulonodular pattern (yes/no)	7 (9) / 70 (91)	4 (57.1) / 17 (24.2)	0.083	
Traction bronchiectasis (yes/no)	5 (6.4) / 72 (93.6)	I (20) / 20 (27.7)	0.999	
Mosaic perfusion (yes/no)	5 (6.4) / 72 (93.6)	1 (20) / 21 (29.1)	0.999	
Consolidation (yes/no)	5 (6.4) / 72 (93.6)	I (20) / 20 (%27.7)	0.999	
Honeycomb lung (yes/no)	4 (5.1) / 73 (94.9)	I (20) / 20 (27.3)	0.999	

normality detected in HRCT was  $1.8\pm0.6 \times 10^3$ /ml and that of cases without parenchymal abnormality was  $2\pm0.9 \times 10^3$ 



**Figure 1.** A curve demonstrating a positive correlation between ALCs and DLCO% values.

 $10^3$ /ml (p=0.434). Lymphopenia was present in 16 (27.1%) of the cases with parenchymal abnormality detected in HRCT and in 5 (27.7%) of the cases without parenchymal abnormality (p=0.999) (Table 6).

When the treatment characteristics of the cases were examined, treatment was not maintained in 77 patients with sarcoidosis included in the study. Sixty (77.9%) cases were followed-up without any treatment and 17 (22.1%) cases had previously received treatment for sarcoidosis. Among these 17 patients, 14 had received oral corticosteroids and 3 received oral corticosteroids together with methotrexate. Five (29.4%) of the 17 treated patients, and 16 of 60 (26.6%) patients who did not receive treatment had lymphopenia. No statistically significant difference was found between the two groups (p=0.824).

#### **DISCUSSION**

In this study, clinical, radiological, and laboratory findings of 77 patients with sarcoidosis were evaluated. The number of lymphopenic cases in the sarcoidosis group was significantly higher than in the control group. There was a corre-

lation between ALCs and DLCO% values in patients with sarcoidosis. Lymphopenic patients with DLCO values less than 80% were more numerous (p=0.01). No significant relationship was found between the stages of sarcoidosis, symptoms, radiological findings, and ALCs (p>0.05). Non-calcified granulomas characterized with the accumulation of CD4 and CD8 T lymphocytes, B lymphocytes, monocytes, mast cells, fibroblasts, and mononuclear phagocytes are seen in the organ affected by sarcoidosis.<sup>[8,15-17]</sup>

In sarcoidosis, the presentation of antigen-presenting cells to CD4 T lymphocytes and cytokines induced by CD4 T lymphocytes triggers granuloma formation. In sarcoidosis, lymphocytes play an important role in the initiation and maintenance of the disease process. As both the lymphocytes are involved in the formation of granulomas and are found in granulomas, these cells are consumed. Therefore, lymphopenia is common in sarcoidosis.<sup>[18–20]</sup> In our study, the number of lymphopenic cases was significantly higher in the sarcoidosis group than in the control group, which is in accordance with the literature findings (p=0.001).

Diffusion of gases through the alveolocapillary membrane in the lungs is measured by the DLCO test. DLCO decreases in diseases affecting the lung parenchyma and alveolocapillary membrane. [21] Studies have shown that DLCO decreased in patients with sarcoidosis with proven pulmonary parenchymal involvement. [22]

In patients with sarcoidosis, DLCO is used in the decision-making process of treatment and also in the evaluation of response to treatment.<sup>[23]</sup> Sweiss et al.<sup>[3]</sup> found that patients with sarcoidosis were significantly more lymphopenic compared to the control group. In their study, lymphopenia was significantly more frequently detected in patients with sarcoidosis who had severe organ system involvement (p<0.05). The authors believed that this was due to the depletion of lymphocytes in the peripheral blood due to infiltration of target organs. Some researchers have suggested that the presence of lymphopenia in sarcoidosis is an indicator of poor prognosis.<sup>[24,25]</sup>

Jones et al.[26] showed that lymphopenia was more frequent in patients with uveitis associated with sarcoidosis and demonstrated that lymphopenia was an independent predictor of the presence of uveitis. As in most interstitial lung diseases (ILDs), in the initial stage of the sarcoidosis alveolitis manifested by the accumulation of various inflammatory and immune effector cells in the alveolar structures, an alveolocapillary unit and interstitium are seen. Various types of cells accumulate in the alveolitic phase of different interstitial lung diseases (ILDs).[27-29] The dominant cells in sarcoidosis are alveolitic T lymphocytes. In different disease states, alveolitic cells may be different, or in sarcoidosis cases, the number of lymphocytes that accumulate in alveolar structures at different periods of the disease or the cells involved in different stages of granulomas may also vary.[30,31]

In our study, we believe that the cause of increased incidence of lymphopenia in patients with low DLCO is decreased lymphocyte counts in peripheral blood due to accumulation of lymphocytes in the interstitium, alveolar structures, and alveolocapillary membranes. Although we cannot prove it histopathologically, this result obtained in our study suggests that sarcoidosis cases in which lymphopenia is detected may be in an alveolitic phase. This result we arrived at is an unproven hypothesis. This assertion can be demonstrated by studies to be performed with bronchoalveolar lavage and transbronchial biopsies in patients with lymphopenic sarcoidosis.

Sakthivel et al.<sup>[31]</sup> more frequently detected radiological features of fibrosis in cases with a decreased number of CD11 T lymphocytes in peripheral blood. Sweiss et al.<sup>[3]</sup> demonstrated higher incidence of lymphopenia in patients with sarcoidosis with severe organ involvement (cardiac, ocular, and neurological) and in patients with advanced lung involvement and FVC <40%. Ocal et al.<sup>[32]</sup> evaluated HRCT findings of sarcoidosis cases and calculated the radiological severity and prevalence scoring of the disease and found correlations among the neutrophil to lymphocyte ratio, radiological severity, and prevalence of the disease. When examining the literature, lymphopenia is found to be observed more frequently in sarcoidosis cases with radiological prevalence. Our study contradicts with the literature in this sense.

We did not find any statistical difference between the presence of radiological abnormalities in HRCTs and the rate of lymphopenia in our cases. One of the reasons for this may be our scarce number of cases and cases in radiological subgroups. One reason is that DLCO testing may be more sensitive to changes in the alveolocapillary region relative to HRCT. Carrington et al.[33] showed that there may be 10 to 30 ml/min/mmHg reduction in the DLCO value due to exercising in patients with non-parenchymal sarcoidosis detected in radiological examination, which suggests that the alveolocapillary membrane may be involved/affected without any sign of parenchymal involvement reflected on HRCT. Another reason is that HRCT, which is used as the gold standard investigation for evaluating lung parenchymal involvement, may be used due to the fact that it is not so sensitive in demonstrating parenchymal involvement.[34] Mostard et al.[35] reported that PET-CT was superior to HRCT in demonstrating inflammatory activity in parenchymal areas in patients with sarcoidosis.

Our study is a retrospective study performed with a relatively few number of cases and reflects the experience of a single center. Therefore, the results cannot be generalized. One of the limitations of the study is that the absence of lymphopenia, which is expected to be seen in the presence of radiological abnormality, was not sufficiently clarified. However, this result may be important, because it may inspire new studies which will requestion the position of the two most important investigations (DLCO and HRCT) currently considered in the assessment of parenchymal involvement of the lung.

Another limitation is that bronchoscopy and especially BAL findings of the cases are not included in the study.

156 South. Clin. Ist. Euras.

Studies in which the numbers of lymphocytes in peripheral blood and BAL fluids were compared with HRCT and DLCO test results may further illuminate this issue.

In conclusion, a decreased number of lymphocytes can be seen in peripheral blood in patients with sarcoidosis and this decrease is related to the DLCO values. Lymphocyte count in peripheral blood is a cheap, easily accessible, and reproducible parameter. More extensive studies are needed on its usability as an activation parameter in the follow-up of sarcoidosis cases and its relationship with prognosis.

#### **Ethics Committee Approval**

Approved by the local ethics committee.

**Informed Consent** 

Retrospective study.

Peer-review

Internally peer-reviewed.

#### **Authorship Contributions**

Concept: C.D., S.Ş.C.; Design: C.D., B.Ç.; Supervision: N.K., E.T.P.; Fundings: A.F., S.B.S.; Materials: A.F., S.B.S.; Data: R.D., B.Ç.; Analysis: S.Ş.C., N.K.; Literature search: N.K.; Writing: C.D.; Critical revision: R.D., B.Ç.

Conflict of Interest

None declared.

### **REFERENCES**

- Wijsenbeek MS, Culver DA. Treatment of Sarcoidosis. Clin Chest Med 2015;36:751–67. [CrossRef]
- Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med 2007;357:2153–65. [CrossRef]
- Sweiss NJ, Salloum R, Gandhi S, Alegre ML, Sawaqed R, Badaracco M, et al. Significant CD4, CD8, and CD19 lymphopenia in peripheral blood of sarcoidosis patients correlates with severe disease manifestations. PLoS One 2010;5:e9088. [CrossRef]
- Laviolette M, La Forge J, Tennina S, Boulet LP. Prognostic value of bronchoalveolar lavage lymphocyte count in recently diagnosed pulmonary sarcoidosis. Chest 1991;100:380–4. [CrossRef]
- James DG, Rizzato G, Sharma OP. Bronchopulmonary lavage (BAL).
   A window of the lungs. Sarcoidosis 1992;9:3–14.
- Bilir M, Sipahi S, Çağatay T, Yanardağı H, Mert A, Demirci S, et al. 100 Sarcoidosis patients: Clinical, features, Diagnosis and prognosis. Eurasian J Pulmonol 1999;1:22–9.
- Topilsky M, Shohat B, Spitzer S, Joshua H. Relationship between T-rosette-forming cells and cellular immunity in sarcoidosis. Ann N Y Acad Sci 1976;278:108–15. [CrossRef]
- Kataria YP, LoBuglio AF, Bromberg PA, Hurtubise PE. Sarcoid lymphocytes: B- and T-cell quantitation. Ann N Y Acad Sci 1976;278:69–79. [CrossRef]
- Bruschi M, Howe JS. Classification of the hematologic variations and abnormalities associated with Boeck's sarcoid; report of a case of thrombocytopenic purpura associated with sarcoidosis, review of the literature and report of a case of thrombocytopenic purpura associated with sarcoidosis, with recovery following splenectomy. Blood 1950;5:478–90.
- Mayock RL, Bertrand P, Morrison CE, Scott JH. Manifestations Of Sarcoidosis. Analysis Of 145 Patients, With A Review Of Nine Series

- Selected From The Literature. Am J Med 1963;35:67–89. [CrossRef]
- Tannenbaum H, Rocklin RE, Schur PH, Sheffer AL. Immune function in sarcoidosis. Studies on delayed hypersensitivity, B and T lymphocytes, serum immunoglobulins and serum complement components. Clin Exp Immunol 1976;26:511–9.
- 12. Selroos O, Koivunen E. Prognostic significance of lymphopenia in sarcoidosis. Acta Med Scand 1979;206:259–62. [CrossRef]
- Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al.; ATS/ERS Task Force. Standardisation of spirometry. Eur Respir J 2005;26:319–38. [CrossRef]
- Standardization of Spirometry, 1994 Update. American Thoracic Society. Am J Respir Crit Care Med 1995;152:1107–36. [CrossRef]
- Soler P, Basset F. Morphology and distribution of the cells of a sarcoid granuloma: ultrastructural study of serial sections. Ann N Y Acad Sci 1976;278:147–60. [CrossRef]
- Rossi G, Cavazza A, Colby TV. Pathology of Sarcoidosis. Clin Rev Allergy Immunol 2015;49:36–44. [CrossRef]
- 17. Ma Y, Gal A, Koss MN. The pathology of pulmonary sarcoidosis: update. Semin Diagn Pathol 2007;24:150–61. [CrossRef]
- Forman JD, Klein JT, Silver RF, Liu MC, Greenlee BM, Moller DR. Selective activation and accumulation of oligoclonal V beta-specific T cells in active pulmonary sarcoidosis. J Clin Invest 1994;94:1533–42.
- Klein JT, Horn TD, Forman JD, Silver RF, Teirstein AS, Moller DR. Selection of oligoclonal V beta-specific T cells in the intradermal response to Kveim-Siltzbach reagent in individuals with sarcoidosis. J Immunol 1995;154:1450–60.
- Davies BH, Williams JD, Smith MD, Jones-Williams W, Jones K. Peripheral blood lymphocytes in sarcoidosis. Pathol Res Pract 1982;175:97–109. [CrossRef]
- Hsia CC, Hyde DM, Weibel ER. Lung Structure and the Intrinsic Challenges of Gas Exchange. Compr Physiol 2016;6:827–95. [CrossRef]
- Young RL, Lordon RE, Krumholz RA, Harkleroad LE, Branam GE, Weg JG. Pulmonary sarcoidosis. 1. Pathophysiologic correlations. Am Rev Respir Dis 1968;97:997–1008.
- Mañá J, Rubio-Rivas M, Villalba N, Marcoval J, Iriarte A, Molina-Molina M, et al. Multidisciplinary approach and long-term follow-up in a series of 640 consecutive patients with sarcoidosis: Cohort study of a 40-year clinical experience at a tertiary referral center in Barcelona, Spain. Medicine (Baltimore) 2017;96:e7595. [CrossRef]
- 24. Böttger D. Prognostic significance of lymphopenia in pulmonary sarcoidosis. Z Erkr Atmungsorgane 1977;149:197–201.
- Böttger D. Prognostic evaluation of the absolute lymphopenia during prednisolone therapy of chronic pulmonary sarcoidosis (author's transl). [Article in German] Z Erkr Atmungsorgane 1976;144:39–44.
- Jones NP, Tsierkezou L, Patton N. Lymphopenia as a predictor of sarcoidosis in patients with uveitis. Br J Ophthalmol 2016;100:1393–6.
- Hunninghake GW, Fulmer JD, Young RC Jr, Gadek JE, Crystal RG. Localization of the immune response in sarcoidosis. Am Rev Respir Dis 1979:120:49–57.
- Hunninghake GW, Gadek JE, Kawanami O, Ferrans VJ, Crystal RG. Inflammatory and immune processes in the human lung in health and disease: evaluation by bronchoalveolar lavage. Am J Pathol 1979;97:149–206.
- Hunninghake GW, Gadek JE, Young RC Jr, Kawanami O, Ferrans VJ, Crystal RG. Maintenance of granuloma formation in pulmonary sarcoidosis by T lymphocytes within the lung. N Engl J Med 1980;302:594–8. [CrossRef]
- Keogh BA, Crystal RG. Clinical significance of pulmonary function tests. Pulmonary function testing in interstitial pulmonary disease. What does it tell us? Chest 1980;78:856–65. [CrossRef]
- 31. Sakthivel P, Bruder D. Mechanism of granuloma formation in sarcoidosis. Curr Opin Hematol 2017;24:59–65. [CrossRef]

- Ocal N, Dogan D, Ocal R, Tozkoparan E, Deniz O, Ucar E, et al. Effects of radiological extent on neutrophil/lymphocyte ratio in pulmonary sarcoidosis. Eur Rev Med Pharmacol Sci 2016;20:709–14.
- 33. Carrington CB. Structure and function in sarcoidosis. Ann N Y Acad Sci 1976;278:265–83. [CrossRef]
- 34. Kilicaslan O, Sönmez FT, Gunes H, Temizkan RC, Kocabay K, Sar-
- itas A. Short Term Unscheduled Revisits to Paediatric Emergency Department - A Six Year Data. J Clin Diagn Res 2017;11:SC12–SC15. [CrossRef]
- Mostard RL, Verschakelen JA, van Kroonenburgh MJ, Nelemans PJ, Wijnen PA, Vöö S, et al. Severity of pulmonary involvement and (18) F-FDG PET activity in sarcoidosis. Respir Med 2013;107:439–47.

# Sarkoidozda Görülen Lenfopeni Hastalık Aktivitesi İle İliskilimidir?

Amaç: Bu çalışmada sarkoidoz olgularında tespit edilen lenfopenin hastalık aktivitesi ile ilişkisi incelenmiştir.

Gereç ve Yöntem: Çalışmaya Temmuz 2016–Haziran 2017 tarihleri arasında sarkoidoz tanısı alan olgular ve aynı dönem aktif hastalığı olmayan sağlıklı gönüllüler/aktif hastalık tanısı almayan olgular dahil edildi. Olguların tam kan sayımlarında mutlak lenfosit sayısı (MLS) <1.3 10³/mm³ olanlar lenfopenik kabul edildi. İki grubta lenfopeni görülme oranları birbirleri ile karşılaştırıldı. Sarkoidoz grubunda lenfopenisi olan ve olmayan olguların solunum fonksiyon testi-karbonmonoksit difizyon testi (SFT-DLCO) değerleri ve yüksek rezolüsyonlu bilgisayarlı tomografi (YRBT) bulguları birbirleri ile karşılaştırıldı.

**Bulgular:** Sarkoidoz grubunda 77, kontrol grubunda 41 olgu dahil edildi. Sarkoidoz grubunda lenfopenik olgu sayısı 21 (%27.2) iken kontrol grubunda 1'di (%2.4) (p=0.001). Sarkoidoz grubunda 33 (%28) olgunun DLCO % değeri %80'nin altında iken, 44 olgunun DLCO % değeri %80'nin üstündeydi. Sarkoidoz grubunda DLCO <%80 olan olguların ortalama MLS'si 1.6±0.7 iken, DLCO >%80 olan olguların 2±0.7'di (p=0.016). MLS ile %DLCO arasında pozitif yönde korelasyon tespit edildi (p=0.044, r=0.230). DLCO <%80 olan olguların %42'sinde lenfopeni var iken, DLCO >%80 olan olguların %15'inde lenfopeni vardı (p=0.01). Olguların sarkoidoz evreleri, semptomları ve radyolojik bulgular ile MLS arasında anlamlı ilişki tespit edilemedi (p>0.05).

Sonuç: Sarkoidoz olgularında lenfopeni sık görülür. Lenfopenik sarkoidoz olgularında düşük DLCO değerleri görülebilir.

Anahtar Sözcükler: Karbonmonoksit difizyon testi; lenfopeni; sarkoidoz.