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Effects of radiological extent on neutrophil/lymphocyte ratio in pulmonary sarcoidosis

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Abstract. – OBJECTIVE: Determining the severity of sarcoidosis is based on the clinical and radiological findings of the disease and the changes in pulmonary function test results. On the other hand; studies are ongoing for objective and easy markers in this respect. Neutrophil/lymphocyte ratio (NLR) is shown as a good prognostic marker for inflammation due to tissue damage in recent clinical trials. In this study, we aimed to identify the possible relationship between NLR and radiological extent of sarcoidosis.

PATIENTS AND METHODS: Data of 122 patients included in the study were evaluated retrospectively in terms of age, gender, complete blood count parameters, erythrocyte sedimentation rate (ESR) and radiological findings at the time of diagnosis.

RESULTS: Mean NLR and ESR were significantly different between radiological stages according to chest radiography and also total HRCT score (THS) groups according to parenchymal involvement in thorax tomography (p <0.05). Mean NLR was found to be 1.28 in stage 0, 1.65 in stage 1, 2.88 in stage 2,5.47 in stage 3 and 8.48 in stage 4; 1.63 in THS group 1, 2.01 in group 2, 3.47 in group 3 and 5.46 in group 4. There were statistically significant positive correlations between NLR and WBC, NLR and THS, NLR and ESR, THS and ESR, ESR and platelet, WBC and #neutrophil, WBC and #lymphocyte.

CONCLUSIONS: Our findings suggest that NLR might be used as a prognostic marker in pulmonary sarcoidosis.

Key Words:
Lymphocyte, Neutrophils, Radiology, Sarcoidosis.

Introduction

Sarcoidosis is a systemic disease with unknown etiology, characterized by non-caseating granulomatous inflammation in lung and other organs[1]. Abnormal radiological findings are observed in approximately 85-95% of pulmonary sarcoidosis cases[2,3]. High-resolution computed tomography (HRCT) is superior in evaluation of pulmonary parenchymal lesions compared with Thoracic computed tomography and other imaging techniques[4]. The definite diagnosis of sarcoidosis; is made by clinical, radiological and laboratory findings with demonstrating non-caseating granulomatous inflammation in histopathological examination and exclusion of other causes of granulomatous inflammation[1].

Changes in clinical severity and course are determinative to start therapy in sarcoidosis. However, to determine the severity of this variable clinical coursed disease is based on interpretation of clinical and radiological findings together with the changes in pulmonary functions. On the other hand, there are numerous studies about objective and easy test and markers which may be helpful in this respect[5-8]. CD4/CD8 T lymphocyte ratio in bronchoalveolar lavage (BAL), angiotensin converting enzyme, serum calcium and 24-hour urine calcium are well known markers in clinical follow-up of sarcoidosis[9,10]. In addition to these markers; usefulness of new markers such as serum chitotriosidase, neopterin, lysozyme, β2 microglobulin, the soluble IL-2 receptor (sIL-2R), Krebsvon den lungen-6 (KL-6), YKL-40 (human cartilage glycoprotein 39) markers were investigated and encouraging results were achieved but none of them has not entered routine clinical use yet[11-17]. Hematological changes may also be observed in sarcoidosis. These changes include mild anemia, leukocytosis,

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leukopenia, lymphopenia, eosinophilia and thrombocytopenia[18]. According to recent clinical trials, neutrophil/lymphocyte ratio (NLR), which shows the changes in both neutrophils and lymphocytes, is provided as an objective measurement for hematological parameters and as a good prognostic agent especially for tissue damage due to inflammation. NLR, whose activity was determined in many chronic diseases, is a quick and easy marker for inflammation. While the complete blood count is one of the routine tests of sarcoidosis, it can be said that NLR does not require additional invasive tests for the patient. Regarding the increase of NLR in certain chronic diseases such as malignancies and cardiovascular diseases, many studies indicate that it may be used as a clinical prognostic factor[19-21]. Number of the previous studies about the role of NLR in sarcoidosis is very limited[22,23]. Taking into consideration that these studies only demonstrated the increase of NLR in sarcoidosis compared with the control group and did not investigate the relation of NLR with severity of the disease, significant evidence about the prognostic value of NLR in sarcoidosis is still lacking. In this study, we aimed to identify the possible relationship between NLR and the radiological extent of pulmonary sarcoidosis.

Patients and Methods

Medical data of 157 patients, diagnosed with pulmonary sarcoidosis in our clinic between January 2008 and January 2015, were investigated retrospectively. We obtained approval from Gulhane Military Medical Academy Ethic Committee to use patients' records for our study and patients' confidentiality was maintained. The medical records of 35 patients were excluded from the study because of inadequate and inappropriate medical records. Data of 122 patients, who were included in the study, was evaluated retrospectively in terms of age, gender, complete blood count parameters, erythrocyte sedimentation rate (ESR) and radiological findings at the time of diagnosis. Chest x-ray and thorax HRCT of the patients were evaluated by two pulmonologists and one radiologist, and scoring was performed by taking the average of points given by three specialists. In assessment of chest x-ray, classical radiologic staging system of sarcoidosis was used[24]. Thorax HRCTs of the patients were examined as previously defined[25-27]. The HRCT scoring system of Drent et al[25] which was adapted from Oberstein et al[26] was used. Thorax HRCT sections were investigated for the presence and the extent of determined parenchymal lesions: (1) parenchymal consolidation, (2) ground-glass opacifications, (3) intra-parenchymal nodules, (4) thickening of the bronchovascular bundle and (5) septal and nonseptal lines, Lung parenchyma sections were divided into 6 zones before scoring[27]. Area above the level of main carina was defined as "upper zone", area between the main carina and the beginning of inferior pulmonary vein as "middle zone", and area below the beginning of the inferior pulmonary vein as "lower zone". The degree of radiological involvement was scored as following; no involvement = 0 point, involvement <25% of a lung zone = 1 point, 25%≤ involvement <50% of a lung zone = 2 points, 50%≤ involvement <75% of a lung zone = 3 points, involvement ≥75% of a lung zone = 4 points. Total extent point for each lesion was estimated by summing the points of that lesion obtained from the 6 lung zones[27]. Then, total HRCT score (THS) for each patient was calculated by summing the total extent points of each radiological lesion. Thus, a total extent point between 0-24 was given for each radiological lesion. Subsequently, patients were divided into 4 groups according to the THS results; group 1 (no parenchymal involvement): THS = 0 points; group 2 (mild parenchymal extent): 1≤THS<20; group 3 (moderate parenchymal extent): 21≤THS< 30; group 4 (severe parenchymal extent): THS≥31.

NLRs of the patients were readily calculated from total blood counts by dividing absolute neutrophil count (#neutrophil) to absolute lymphocyte count (#lymphocytes). The obtained data were statistically analyzed using SPSS 20.0 statistical software (SPSS Inc., Chicago, IL, USA). The *p*-value less than 0.05 was considered as statistically significant.

Results

Data of 122 patients were evaluated. 100 (81.97%) patients were male and 22 (18.03%) were female. Mean ages of the cases were 30.61 ± 8,953 (20-70) in males and 42.14 ± 11,585 (25-68) in females. When analyzed in terms of classical radiological stages of the patients due to chest X-ray, 12 (9.83%) cases were found to be stage 0, 47 (38.52%) were stage 1, 38

Table I. Mean values of parameters due to classical radiological stages.

	n (%)	age	THS	WBC	#neut.	#lymp.	NLR	ESR	HGB	PLT (10^3)
Stage 0	12 (9.8%)	31 (±12.9)	**10.41 (±7.8)**	7116 (±1195)	3539 (±691)	**2751 (±488)**	**1.28 (±0.09)**	**17.7 (±17.1)**	14.1 (±2.0)	282 (±58)
Stage 1	47 (38.5%)	31.64 (±8.1)	**18.03 (±8.8)**	6238 (±1602)	3667 (±972)	**2245 (±608)**	**1.65 (±0.17)**	**17.1 (±6.8)**	14.9 (±1.4)	269 (±56)
Stage 2	38 (31.1%)	32.54 (±10.9)	**23.48 (±11.9)**	6632 (±1466)	4526 (±1062)	**1637 (±469)**	**2.88 (±0.80)**	**20.7 (±9.5)**	14.5 (±1.7)	275 (±65)
Stage 3	21 (17.2%)	34.04 (±11.1)	**30.95 (±11.4)**	6938 (±1554)	5392 (±1449)	**1131 (±582)**	**5.47 (±1.98)**	**23.4 (±7.7)**	14.7 (±1.2)	270 (±58)
Stage 4	4 (3.2%)	45 (±15.4)	**30.75 (±7.7)**	8400 (±668)	7125 (±518)	**850 (±100)**	**8.48 (±1.22)**	**27 (±7.7)**	14.2 (±2.0)	243 (±123)

(31.15%) were stage 2, 21(17.21%) were stage 3 and 4 (3.27%) were stage 4. Mean THSs of the cases was 19.13 ± 12.37 (0-56). While 13 (10.65%) cases were found to have no radiological lesion and evaluated in THS group 1, 57 (46.72%) cases were found to be in THS group 2, 33 (27.05%) in THS group 3 and 19 (15.57%) in THS group 4. Number of cases with mean values (± standard deviation) of age, THS, white blood cell (WBC), #neutrophil, #lymphocyte, NLR, ESR, hemoglobin and platelet counts were summarized for each classical radiological stage and THS group in Table I and II respectively (Table I and II). Mean NLR results were determined as 1.28 in stage 0, 1.65 in stage 1, 2.88 in stage 2, 5.47 in stage 3 and 8.48 in stage 4; and in terms of THS groups mean NLR results were found to be 1.63 in THS group 1, 2.01 in THS group 2, 3.47 in THS group 3 and 5.46 in THS group 4. Differences of mean NLR values between radiological stages and THS groups were statistically significant ($p < 0.001$). In addition to NLR; THS, #lymphocyte and ESR averages also showed significant differences between radiological stages ($p < 0.001$, $p < 0.001$, $p = 0.004$); and, mean #lymphocyte and ESR values also showed significant differences between THS groups ($p < 0.001$, $p < 0.001$, $p = 0.009$). The relations and possible correlations of all parameters were examined carefully. In statistically assessment of variables, Kolmogorov-Smirnov, Shapiro-Wilk, Skewness and Kurtosis normality tests were used to determine if data were well-modeled by a normal distribution[28,29]. Because ESR did not show normal distribution in all normality tests it

Table II. Mean values of parameters due to THS groups.

	n (%)	age	WBC	#neut.	#lymp.	NLR	ESR	HGB	PLT (10^3)
THS-1	13 (10.7%)	34.38 (±10.6)	6784 (±1418)	3828 (±838)	2384 (±569)	1.63 (±0.28)	19.4 (±8.9)	13.9 (±1.8)	287 (±44)
THS-2	57 (46.7%)	34.33 (±10.5)	6529 (±1365)	3899 (±924)	2161 (±704)	2.01 (±1.01)	17.8 (±9.7)	14.5 (±1.6)	273 (±59)
THS-3	33 (27%)	32.09 (±10.6)	6221 (±1579)	4405 (±1336)	14831 (±615)	3.47 (±1.86)	23.1 (±9.6)	14.9 (±1.4)	284 (±67)
THS-4	19 (15.6%)	32.78 (±10.1)	7678 (±1645)	5924 (±1463)	1308 (±659)	5.46 (±2.43)	22.3 (±6.8)	14.8 (±1.3)	253 (±65)

was evaluated by Spearman's correlation analysis, while the other parameters with normal distribution were evaluated by Pearson correlation analysis.

There were statistically significant positive correlations between NLR and WBC (r=0.225, p=0.013), NLR and THS (r=0.555, p<0.001), NLR and ESR (r=0.323, p<0.001), THS and ESR (r=0.223, p=0.013), ESR and platelet (r=0.197, p=0.029), WBC and #neutrophil (r=0.819, p<0.001), WBC and #lymphocyte (r=0.451, p<0.001). On the other hand, significant negative correlations were existing between ESR and #lymphocyte r= -0.310, p=0.001), ESR and hemoglobin (r= -0.236, p=0.009), and hemoglobin and platelet (r= -0.320, p<0.001).

Discussion

Investigations on new prognostic markers on sarcoidosis such as serum chitotriosidase, neopterin, lysozyme, β2 microglobulin, the soluble IL-2 receptor (sIL-2R), Krebsvon den lungen-6 (KL-6), YKL-40 (human cartilage glycoprotein 39) are going on currently[11-17,30]. Despite the achievement of positive results with such markers, these methods require additional tests for the patient, some specific laboratory kits and more time. In this point, if the possible hematologic and inflammatory changes that may be observed in sarcoidosis were also taken into account; NLR, which can be easily calculated from complete blood count, may be crucial in the assessment of sarcoidosis[19,21,23,24].

Lymphocytic alveolitis is a striking feature of sarcoidosis in terms of immune cell changes[31]. Despite the increased inflammation in the area of concentrated granulomas, peripheral anergy is a specific immune paradox of sarcoidosis. This phenomenon is considered to be associated with the imbalance of effector and regulatory T lymphocytes. Regulatory cells ($CD4^+$, $CD25^{bright}$, Fox P3+) accumulate in the periphery of the granulomas and peripheral blood, and show anti-proliferative effects on T lymphocytes in active disease[31]. Another opinion in this issue is that peripheral lymphopenia occurs due to the concentration of T lymphocytes in infected regions[18]. In addition, significantly higher activation of CD4 and CD8 T-lymphocytes in bronchoalveolar lavage rather than peripheral blood was demonstrated by flow-cytometric methods with *ex-vivo* studies[10,18,31]. Gupta et al[18] stated that lymphopenia exists in 26.66% of sarcoidosis patients and the most common hematologic abnormality was also the lymphopenia in their work.

Neutrophils are the precursor cells of inflammation in tissue damage and the main triggers of inflammatory processes and thrombosis. Conversely, lymphocytes play role more specifically in specific immunity rather than tissue damage[19,21,32]. In myocardial infarction, characterized by inflammation and tissue damage, negative correlation was observed between ejection fraction and the number of neutrophils[33]. The decrease in lymphocyte rates in inflammatory pathologies may be associated with elevated plasma cortisol levels due to increased stress and apoptosis[21,32]. NLR, which represents the changes in both of these hematological parameters, is considered as a recent significant prognostic marker of some diseases characterized by inflammation and oxidative stress[19,32,33]. However, in the literature, we met very limited number of researches focused on the role of NLR in sarcoidosis[22,23]. In the study of Dirican et al[23], NLR was observed higher in sarcoidosis patients rather than the control group and the mean NLR value was found to be higher in patients with extrapulmonary involvement. Iliaz et al[22] investigated the possible role of NLR in the differential diagnosis of sarcoidosis and tuberculosis and showed that mean NLR value was higher in tuberculosis cases compared to the sarcoidosis cases. They also demonstrated that higher mean NLR value exists in sarcoidosis patients rather than the control group.

When we detected the literature in terms of the role of ESR in sarcoidosis and the relationship between ESR and NLR, we found that higher mean ESR values were reported in sarcoidosis compared to the healthy control group[18]. Dirican et al[23] stated that there was a positive correlation between ESR with radiological stage and NLR in sarcoidosis patients in their study. Consistent with the literature, in our report, mean ESR values showed significant differences between groups in terms of classical radiological stages and THS groups, and also higher mean ESR values were determined by the radiological extent increases. In addition, a positive correlation was observed between NLR and ESR in our results.

THS, a method referenced in the radiological assessment of lung diseases, provides numerical scoring and classification facilities about the extent and the severity of parenchymal involvement[25-27]. Ors et al[27] used THS in their work and compared the results in terms of pulmonary func-

tion test results in sarcoidosis cases. They stated that there were significant correlations between pulmonary function parameters and HRCT pattern scores, and also between chest-x-ray and total HRCT scores. Our study results also demonstrated a correlation between THS and THS groups with classical radiological stages determined with chest x-ray. This situation reveals the acceptability of THS measurement as a reliable objective radiological assessment method. In this respect, comparing the parameters examined in our study among both radiological stages and THS groups is seen as a feasible approach. Considering the statistically significant differences of mean NLR and ESR values among both of radiological stages and THS groups, we suggest that NLR and ESR can be evaluated as indicators of the radiological extent of pulmonary sarcoidosis.

Conclusions

NLR can be used as a prognostic marker in sarcoidosis. In order to demonstrate the effectiveness of NLR in sarcoidosis more accurately, prospective studies including clinical findings in addition to the radiological findings are needed.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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