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Can hematological parameters guide the differentiation between sarcoidosis and tuberculous lymphadenitis?

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Abstract:

BACKGROUND: Tuberculosis (TB) and sarcoidosis, which are considered two different ends of the same disease spectrum, usually cannot be differentially diagnosed based on laboratory tests and radiological imaging. Clinical, histopathological, and bacteriological examinations as well as response to treatment can guide diagnosis. The aim of this study was to examine correlations between hematological parameters and disease in patients who were diagnosed with sarcoidosis, TB, or reactive lymphadenopathy (LAP) after mediastinoscopy.

MATERIALS AND METHODS: The study included a total of 223 patients diagnosed with either reactive LAP ($n = 65$), sarcoidosis ($n = 83$), or TB ($n = 75$) after mediastinoscopy between September 2012 and May 2017. The patient groups were retrospectively evaluated in terms of demographic characteristics, complete blood count parameters, erythrocyte sedimentation rate, and radiological findings.

RESULTS: Sedimentation rate and platelet count were significantly higher in TB patients compared with sarcoidosis ($P = 0.001$, $P = 0.011$) and reactive LAP patients ($P = 0.001$, $P = 0.001$). Lymphocyte count was significantly higher in patients with reactive LAP than in patients with TB and sarcoidosis ($P = 0.001$, $P = 0.001$). Platelet/lymphocyte ratio (PLR) was significantly higher in TB patients compared to those with sarcoidosis and reactive LAP ($P = 0.001$, $P = 0.001$) and in sarcoidosis patients compared to reactive LAP patients ($P = 0.001$). Neutrophil/lymphocyte ratio (NLR) values in the TB and sarcoidosis groups were significantly higher than that of the reactive LAP group ($P = 0.001$, $P = 0.012$). Stage 2 sarcoidosis patients were found to have significantly higher PLR, NLR, and platelet count compared to Stage 1 patients ($P = 0.001$, $P = 0.01$, $P = 0.009$).

CONCLUSION: PLR and NLR can be used to discriminate patients with sarcoidosis and TB from patients with reactive LAP. In addition, PLR may also serve as a guiding parameter in the differentiation between tuberculous LAP and sarcoidosis.

Keywords:

lymphadenopathy, mediastinoscopy, sarcoidosis, tuberculosis

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Introduction

The differential diagnosis of granulomatous lung diseases is among the most challenging differentials for clinicians. Granulomatous inflammation of the lung is characterized by focal lesions comprising activated macrophages and lymphocytes within a network of matrix proteins. These lesions, called granulomas, are an important defense mechanism against mycobacterial and fungal infections but may also arise due to noninfectious causes. The leading noninfectious cause is sarcoidosis, the etiology of which is not completely understood.[1]

Tuberculosis (TB) is among the leading causes of granulomatous disorders in developing countries. TB preferentially affects the lungs but can involve all organs and systems. Lymph node TB is the most common form of extrapulmonary TB.[2,3]

Sarcoidosis is most commonly confused with TB in pathological differentiation. Sarcoidosis is an autoimmune disease that can involve many organs and systems and is histopathologically characterized by noncaseating granulomatous inflammation. The most well-known feature of sarcoidosis is its involvement of the respiratory system, especially the lungs. A multidisciplinary (laboratory, clinical, and radiological) evaluation of mediastinal lymphadenopathy (LAP) biopsy is important in the diagnosis of Stage 1 and 2 sarcoidosis.[4,5] However, despite advanced tests for granulomatous lymphadenitis, TB and sarcoidosis can still be confused for one another.

The platelet/lymphocyte ratio (PLR) and neutrophil/lymphocyte ratio (NLR) have been associated with clinical course, prognosis, and mortality in malignancy, rheumatoid arthritis, cardiovascular diseases, pulmonary embolism, and many inflammatory diseases.[6-8] In separate studies on patients with sarcoidosis and TB, it was observed that PLR and NLR increased with sarcoidosis stage and were higher than in the healthy control group, whereas in TB patients, a significant relationship was only observed with NLR.[9,10] There is no previous study evaluating hematologic parameters in patients with TB, sarcoidosis, and reactive lymphadenitis in the literature.

The aim of the present study was to examine the relationships between disease and hematological parameters in patients who were clinically, radiologically, and histopathologically diagnosed with sarcoidosis, TB, and reactive LAP following mediastinoscopy.

Materials and Methods

This retrospective study included 237 patients who underwent lymph node biopsy by mediastinoscopy. Between 2012 and 2017, 79 caseating granulomatous inflammation samples, 91 noncaseating granulomatous inflammation samples, and 67 reactive lymphoid tissue samples were obtained from these patients during follow-up and treatment. Patients with active lung parenchymal involvement, diagnosis of granulomatous inflammation, or indefinite diagnosis due to conflicting findings during follow-up were excluded. Eight patients who were initially diagnosed with noncaseous granulomatous lymphadenitis and later diagnosed with Hodgkin's or non-Hodgkin's lymphoma during follow-up and two patients who were diagnosed with reactive lymph nodes and were found to have malignancy during follow-up were not included in the study. We also excluded four patients with caseous necrosis but no follow-up records [Figure 1]. Diagnosis of tuberculous lymphadenitis was based on a multidisciplinary evaluation following mediastinoscopy and histopathological and bacteriological examinations. Twelve of the patients diagnosed with tuberculous lymphadenitis exhibited a suspicious tree-in-bud sign suggestive of pulmonary TB, but acid-fast bacilli did not appear or grow in direct inspection and culture of bronchoalveolar lavage obtained from the site. Patients diagnosed as having extrapulmonary tuberculous lymphadenitis showed no signs of pulmonary TB and no other organ involvement that might be attributed to extrapulmonary TB. For patients histopathologically diagnosed as having nonnecrotizing granulomatous lymphadenitis, other diseases characterized by granulomatous lymphadenitis, primarily TB, were first ruled out, and then, based on clinical and radiologic findings, the diagnosis of sarcoidosis was established.

Sarcoidosis patients were staged based on chest X-ray findings: hilar LAP as Stage 1 and hilar LAP and parenchymal involvement as Stage 2. Patients with

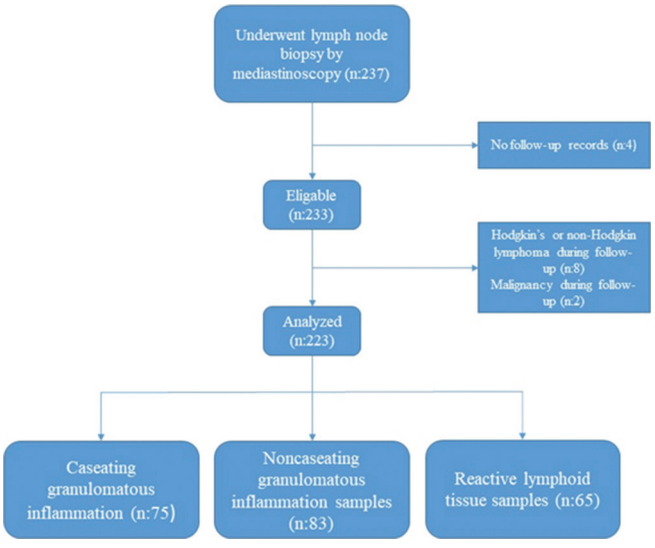

Figure 1: Grouping of patients after mediastinoscopy

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reactive LAP who did not develop any additional pathology during follow-up were included in the study. During the study period, first bronchoscopic transbronchial needle aspiration (TBNA) and later mediastinoscopy were used as the primary approach to mediastinal LAP. Because more patients were diagnosed by mediastinoscopic biopsy than by TBNA, we retrospectively evaluated this patient group.

Informed written consent was obtained from all patients included in the study, and a local ethics committee approved the study design (B.30.2.ATA.0.01.00/23).

Cervical mediastinoscopy procedure

In our center, mediastinoscopies are performed after the intubation of the patients. After cleaning the surgical site, a 3-cm horizontal incision was made in the cervical region approximately 2 cm above the suprasternal notch. The skin, subcutaneous layers, and fascia of the neck were dissected to access the strap muscles. The pretracheal fascia was exposed by splitting the strap muscles. The pretracheal fascia was incised, and a video-mediastinoscopy device (Storz) was inserted. Samples were obtained from mediastinal stations 2R, 4R, 2L, 4L, and 7, depending on the location of the patient's lesion. Samples were taken from at least one and at most four stations.

Whole blood and inflammatory marker assessment

Hematologic data of the patients were obtained at initial diagnosis. In our center, complete blood count is analyzed by impedance/spectrophotometry (Beckman Coulter LH 780 Analyzer; Beckman Coulter, Inc., CA, USA). Hematological parameters (leukocyte count, neutrophil count, hemoglobin, platelet count, NLR, and PLR) at the time of diagnosis were recorded. NLR was calculated as neutrophil count divided by lymphocyte count, and PLR was calculated as platelet count divided by lymphocyte count. Erythrocyte sedimentation rate (ESR) was calculated by the Westergren method.

Statistical analysis

Statistical analysis was performed using SPSS for Windows (version 20.0; SPSS Inc., Chicago, IL, USA). Pearson's Chi-square test was used to compare means between groups. Differences in hemoglobin level, neutrophil count, lymphocyte count, platelet count, PLR, NLR, and ESR between groups were evaluated using one-way analysis of variance [Table 1] and Mann–Whitney-U test [Table 2], and nonparametric data were evaluated using Kruskal–Wallis test. Pearson's correlation analysis was used to evaluate whether PLR and NLR were associated with ESR. Receiver operating characteristic (ROC) curve analysis was used to determine the cutoff value of PLR and NLR levels in the groups. Statistical significance was determined as $P < 0.05$.

Results

Of the 223 patients included in the study, 83 had sarcoidosis, 75 had TB, and 65 had reactive LAP. The mean age was 35.2 ± 12.3 years in the sarcoidosis group, 36.3 ± 18.6 years in the TB group, and 48 ± 27.9 years in the reactive LAP group. The mean age did not differ

Table 1: Comparison laboratory parameters between the patient groups

	Mean±SD			*P**	*P***	*P****
	Reactive LAP (*n*=65)	Tuberculosis (*n*=75)	Sarcoidosis (*n*=83)			
Hemoglobin (g/dL)	13.8±1.3	13.4±2.1	13.6±1.8	0.81	0.74	0.39
Lymphocyte count (/μL)	2411±652.3	1376.9±583.5	1721.3±603.6	0.001	0.001	0.001
Neutrophil count (/μL)	4371.5±1751.8	4962.8±1781.8	5196.5±1915.8	0.7	0.019	0.138
Platelet count (/μL)	233030.8±77316.5	340560.0±173006.6	283139.8±98332.3	0.011	0.041	0.001
PLR	110.6±70.9	274.3±129.9	191.3±124.7	0.001	0.001	0.001
NLR	2.4±2.9	4.1±2.1	3.5±2.4	0.3	0.012	0.001
ESR (mm/hr)	10.1±7.3	27±18.9	17.1±15	0.001	0.001	0.001

*Sarcoidosis versus tuberculosis patients, **Sarcoidosis versus reactive LAP patients, ***Tuberculosis versus reactive LAP patients. ANOVA test was used to compare groups. LAP: Lymphadenopathy, SD: Standard deviation, PLR: Platelet/lymphocyte ratio, NLR: Neutrophil/lymphocyte ratio, ESR: Erythrocyte sedimentation rate, ANOVA: Analysis of variance

Table 2: Age, sex, and number of concomitant diseases in the groups

	Reactive LAP (*n*=65)	Tuberculosis (*n*=75)	Sarcoidosis (*n*=83)
Age (years)	48±27.9	36.3±18.6	35.2±12.3
Sex (male), *n* (%)	48 (73.8)	35 (46.6)	21 (25.3)
Hypertension, *n* (%)	12 (18.7)	2 (2.7)	3 (3.6)
Diabetes mellitus, *n* (%)	5 (7.7)	10 (13.3)	1 (1.2)
Coronary arterial disease, *n* (%)	1 (1.5)	1 (1.3)	-
Chronic obstructive pulmonary disease, *n* (%)	9 (13.8)	8 (10.7)	-
Biomass exposure, *n* (%)	15 (23.1)	6 (8)	2 (2.4)

LAP: Lymphadenopathy

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statistically between the TB and sarcoidosis groups but was significantly higher in the reactive LAP group compared to both ($P = 0.001$, $P = 0.002$).

There were 59 females and 24 males in the sarcoidosis group, 44 females and 31 males in the TB group, and 7 females and 58 males in the reactive LAP group. Sex distribution differed significantly among the groups ($P = 0.001$).

Evaluation of the laboratory parameters of the patients included in the study is shown in Table 1. There was no statistically significant difference in hemoglobin levels between the groups. In pairwise comparisons, lymphocyte count was significantly higher in patients with reactive LAP compared to patients with sarcoidosis and TB ($P = 0.001$, $P = 0.001$) and in sarcoidosis patients compared to TB patients ($P = 0.001$). Neutrophil count was only significantly higher in the sarcoidosis group compared to the reactive LAP group ($P = 0.019$). Platelet count was significantly higher in TB patients than in patients with sarcoidosis and reactive LAP ($P = 0.011$, $P = 0.001$) and in sarcoidosis patients compared to patients with reactive LAP ($P = 0.041$). ESR was significantly higher in TB patients compared to patients with sarcoidosis and reactive LAP ($P = 0.001$, $P = 0.001$) and in the sarcoidosis group compared to the reactive LAP group ($P = 0.001$). Age, sex, and number of concomitant diseases in the groups are shown in Table 2. The prevalence of diabetes mellitus was higher in the TB lymphadenitis group compared to other groups, whereas hypertension was more common among patients with reactive LAP than in the other groups.

Similarly, PLR was also significantly higher in TB patients compared to patients with sarcoidosis and reactive LAP ($P = 0.001$, $P = 0.001$) and in sarcoidosis patients compared to reactive LAP patients ($P = 0.001$). NLR values in the TB and sarcoidosis groups were not statistically different ($P = 0.3$) but were significantly higher than that of the reactive LAP group ($P = 0.001$, $P = 0.012$). ESR of the groups was significantly correlated with their PLR ($r = 0.718$, $P = 0.001$) and NLR ($r = 0.499$, $P = 0.001$) values.

In the sarcoidosis group, 40 patients were classified as Stage 1 and 43 as Stage 2. The age and laboratory values of patients with Stage 1 and 2 sarcoidosis are shown in Table 3. When these two groups were compared, patients with Stage 1 sarcoidosis had significantly higher lymphocyte count ($P = 0.001$). In contrast, Stage 2 patients had significantly higher PLR, NLR, and platelet count compared to Stage 1 patients ($P = 0.001$, $P = 0.01$, $P = 0.009$).

In ROC curve analysis of PLR in TB and sarcoidosis patients, the area under the curve was 0.69 (95% confidence interval [CI]: 62–78) [Figure 2]. At a cutoff value of 207.1, PLR had a sensitivity of 60% and specificity of 75% in the diagnosis of TB. In ROC curve analysis of PLR and NLR in patients who developed granulomatous lymphadenitis and patients with reactive LAP, the areas under the curves were 0.85 and 0.79, respectively (CI: 80–91, CI: 71–86) [Figure 3]. At cutoff values of 152.1 for PLR and 2.3 for NLR, sensitivity was 66% and 77% and specificity was 88% and 80%, respectively.

Discussion

In this study, our comparison of PLR and NLR in sarcoidosis and TB – two important etiologies of granulomatous lymphadenitis – and in reactive LAP revealed that PLR and NLR were higher in patients with granulomatous lymphadenitis. We also found that PLR was higher in patients with TB compared to patients with sarcoidosis. When patients with Stage 1 and 2 sarcoidosis were compared, PLR and NLR were higher Stage 2 sarcoidosis.

Regardless of the cause of granulomatous diseases, their basic pathogenetic mechanisms are similar. In TB, tubercles form in the center of granulomas, typically as a result of caseous necrosis. The macrophages in the granuloma have typically turned into epithelioid cells. In sarcoidosis, however, true caseous necrosis is absent, but there may be small areas of eosinophilic necrosis. Later, epithelioid cells are dispersed with developing fibroblastic connective tissue cells and collagen tissue

Table 3: Comparison of age and laboratory values of patients with Stage 1 and 2 sarcoidosis

	Mean±SD		*P*
	Stage 1 sarcoidosis (*P*=40)	Stage 2 sarcoidosis (*P*=43)	
Age (years)	34±15.1	36.3±11.4	0.438
Hemoglobin (g/dl)	13.3±1.76	13.7±1.8	0.329
Lymphocyte count (/μL)	1954.3±588.7	1504.7±538.4	0.001
Neutrophil count (/μL)	4797.5±1616.3	5565.8±2109.1	0.065
Platelet count (/μL)	254,600.0±64,279.6	309,688.4±116,378.6	0.009
PLR	146.7±91.8	232.8±137.3	0.001
NLR	2.8±2.2	4.2±2.4	0.01
ESR (mm/h)	11.4±10.1	22.5±16.9	0.001

Mann–Whitney U-test was used to compare groups. SD: Standard deviation, PLR: Platelet/lymphocyte ratio, NLR: Neutrophil/lymphocyte ratio, ESR: Erythrocyte sedimentation rate

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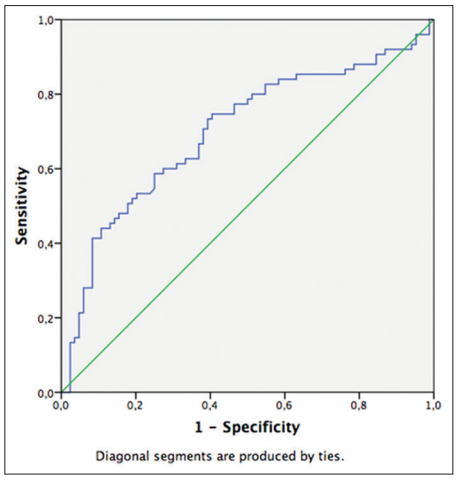

Figure 2: Receiver operating characteristic curve analysis of platelet-to-lymphocyte ratio in patients with tuberculosis and sarcoidosis

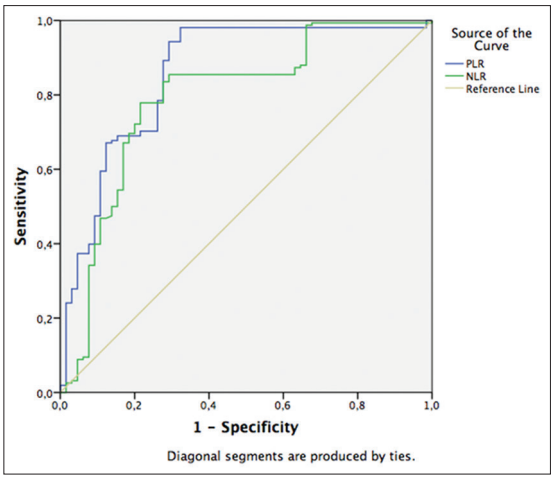

Figure 3: Receiver operating characteristic curve analysis of platelet-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio in patients with reactive lymphadenopathy and granulomatous lymphadenitis

develops. The cytoplasm of giant cells may contain Schaumann bodies, asteroid bodies, and some inclusion bodies made of centrospheres.[11] In patients with no caseous necrosis in the granulomas, the differential diagnosis of TB and sarcoidosis cannot be established morphologically.[12,13]

Various parameters such as purified protein derivative test, serum angiotensin-converting enzyme level, soluble interleukin-2 receptor level, and serum amyloid A level have been used in the differential diagnosis of these very similar conditions. However, these parameters not only fail to clearly differentiate the two diseases, but the high cost of some of the assessments also imposes an economic burden.[1] These problems have led to the use of easily assessed, inexpensive parameters in the differential diagnosis. PLR and NLR are among the most important of these because they are inexpensive and easily obtained in clinical practice.[14-16]

Peripheral lymphopenia has been detected in patients with diseases involving granulomatous infections, such as sarcoidosis and TB. This has been attributed to an increase in lymphocyte density around the granuloma and peripheral lymphopenia secondary to this. This increase is thought to be caused primarily by regulatory and effector T-lymphocyte imbalance. The accumulation of regulatory T-lymphocytes around the granuloma was proposed to have an antiproliferative effect on effector T-lymphocytes.[17,18] In another study of sarcoidosis patients, lymphopenia occurred independently of disease severity and was found to resolve with treatment.[15] A study comparing platelet counts in patients with TB diagnosis confirmed by histopathology and culture and patients with granulomatous inflammation but without culture-confirmed TB diagnosis showed that platelet count was higher in confirmed TB. Degree of thrombocytosis was found to be correlated with ESR and C-reactive protein level, and its etiology was considered secondary to a primary infective pathology.[18]

Studies evaluating PLR and NLR in association with TB and sarcoidosis showed that patients with sarcoidosis had higher PLR and NLR compared to the healthy control group and that this difference increased significantly in correlation with sarcoidosis stage.[10,19] In a study that examined hematological parameters in patients with pulmonary TB, it was reported that NLR may be an important parameter in disease severity and treatment monitoring, whereas no significant results were obtained for PLR. In the evaluation of the relationship between NLR/PLR and ESR in sarcoidosis patients, a weak but significant correlation was observed.[9,10] These previous studies on TB patients focused on parenchymal TB, and we were unable to find any publications regarding tuberculous lymphadenitis or the differential diagnosis of TB, sarcoidosis, and reactive lymphadenitis in the literature. Our study is novel in this respect.

Consistent with other studies, our data demonstrated a significant difference in terms of PLR and NLR between patients with TB and sarcoidosis, which are causes of granulomatous lymphadenitis, and patients with reactive LAP. The significantly higher PLR observed in tuberculous lymphadenitis compared to sarcoidosis has been attributed to the relative proportion of lymphocytes in the granulomas being higher in TB than in sarcoidosis, thereby leading to peripheral lymphopenia. In addition, the elevated ESR in TB patients compared to sarcoidosis patients and the secondary thrombocytosis associated with this may be considered another factor that triggers a rise in PLR. There was a strong correlation between ESR and PLR, while ESR was only moderately correlated with NLR in our study. This indicates that PLR is superior to NLR in the evaluation of inflammatory parameters. The

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higher specificity than sensitivity of PLR and NLR in the ROC curves of patients with TB and sarcoidosis lymphadenitis and in patients with granulomatous lymphadenitis and reactive lymphadenitis suggest that these parameters may be more effective in ruling out diseases.

Due to the inclusion of only patients with sarcoidosis Stage 1 and 2 in this study and the relatively lower sensitivity of PLR and NLR compared to their specificity in the ROC curve analysis, large-scale studies that encompass all stages of sarcoidosis and investigate parameters that may have higher sensitivity are needed.

Conclusion

Differential diagnosis of the main causes of granulomatous lymphadenitis, such as TB and sarcoidosis, can be difficult in spite of the advanced testing currently available. PLR and NLR can be used in the differential diagnosis of reactive lymphadenitis and granulomatous lymphadenitis. In addition, PLR may also be a guiding parameter in the differentiation between tuberculous lymphadenitis and sarcoidosis.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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