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The role of systemic immune-inflammation index (SII) in the differential diagnosis of granulomatous and reactive LAP diagnosed by endobronchial ultrasonography

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Abstract. *Background and aim*: Tuberculosis and sarcoidosis are the two most important granulomatous diseases that physicians have difficulty differentiating. In our study, we aimed to observe the utility of systemic immune-inflammation index (SII) in the differentiation of patients diagnosed by endobronchial ultrasound (EBUS)-guided lymph node biopsy. *Methods*: Our study included 494 patients who presented to the chest diseases outpatient clinic of our hospital between 2015 and 2020 and underwent EBUS-guided biopsy for mediastinal lymphadenopathy (LAP). The patients' pre-procedural hematologic parameters and results of at least 2-year follow-up after diagnosis were retrospectively evaluated. *Results*: When compared by patient group, SII was significantly higher in patients with tuberculous lymphadenitis compared to those with sarcoidosis and reactive LAP (p=0.01 and <0.001, respectively) and in patients with sarcoidosis compared to those with reactive LAP (p=0.002). Among patients with sarcoidosis, platelet count, erythrocyte sedimentation rate, and SII were significantly higher in stage 2 patients compared to stage 1 patients, while lymphocyte levels were lower (p=0.009, 0.001, 0.001, and 0.001 respectively). In the ROC curve analysis of SII between patients with sarcoidosis and tuberculosis LAP, the area under the curve was 0.668. At a cut-off value of 890.7, SII had 70% sensitivity and 66% specificity in the differentiation of tuberculosis and sarcoidosis lymphadenitis. *Conclusion*: SII is an easily obtained parameter that may aid in the differentiation of tuberculosis and sarcoidosis LAP with granuloma and in the differentiation of granulomatous diseases from reactive LAP.

Key words: sarcoidosis, tuberculosis, SII

Introduction

The mediastinum has a rich lymphatic network with numerous lymph nodes. The etiology of mediastinal/hilar lymph node enlargement includes a wide range of diseases such as lymphoma, metastatic carcinoma, sarcoidosis, and tuberculosis (TB) (1). Furthermore, mononuclear inflammatory cell aggregation or "granuloma" formation, a modified macrophage aggregation of epithelial cells often containing multinucleated giant cells and surrounded by a rim of lymphocytes, represents a chronic inflammatory response initiated by various infectious or non-infectious agents (2). As a result, granulomatous mediastinal/hilar lymphadenitis is frequently encountered and clinicians have difficulty differentiating non-infectious causes (3).

The rise in the incidence of HIV infection led to an increase in the use of immunosuppressive agents as well as in the incidence of TB (4). Although TB most commonly causes involvement of the lung tissue, it can present with extrapulmonary involvement in 15% of cases (5). Lymph node TB constitutes the largest proportion of extrapulmonary TB cases. The fact that microbiologic sampling in lymph node

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TB cases is not as easy as in parenchymal TB has increased the frequency of diagnostic interventional procedures (6).

Sarcoidosis is one of the diseases most frequently confused with TB in pathologic differential diagnosis (7). Sarcoidosis is an autoimmune disease of unknown etiology with histopathologically non-caseating granulomatous inflammation that can involve many organs and systems. Sarcoidosis is best known for its involvement of the respiratory system, particularly the lungs (8). Multidisciplinary laboratory, clinical, and radiologic evaluation of mediastinal lymphadenopathy (LAP) biopsy in stage 1 and 2 sarcoidosis is an important part of the diagnosis. However, despite further investigations for granulomatous lymphadenitis, the diagnoses of TB and sarcoidosis can still be confused (9).

Studies evaluating hematologic parameters have used platelet-to-lymphocyte ratio (PLR) and neutrophil-to-lymphocyte ratio (NLR) in the differential diagnosis of these two similar diseases. One study demonstrated that PLR values were higher in patients with tuberculous lymphadenitis compared to patients with sarcoidosis, and both PLR and NLR levels were higher in patients with Stage 2 sarcoidosis compared to patients with Stage 1 sarcoidosis (10).

In our study, we aimed to compare endobronchial ultrasound (EBUS)-guided biopsy results and systemic immune-inflammation index (SII) values between patients with mediastinal LAP clinically and radiologically diagnosed as TB or sarcoidosis and patients with reactive lymph nodes.

Materials and methods

Study design

The study included 494 patients who presented to the chest diseases outpatient clinic of our hospital between 2015 and 2020 and underwent EBUS-guided biopsy for mediastinal LAP. The patient's biopsy results, pre-procedural hematological parameters, and data from at least 2 years of follow-up were retrospectively recorded from the hospital automation system and the national medical data system (e-Nabız).

Study population

Based on the patient's EBUS-guided biopsy results and follow-up data, 22 patients who were found to have non-caseous granulomatous lymphadenitis and were later diagnosed with Hodgkin or non-Hodgkin lymphoma during follow-up and 2 patients found to have reactive lymph nodes who were diagnosed with malignancy during follow-up were excluded from the study. Another 13 patients who had caseous necrosis but missing follow-up data were also excluded. In addition, 176 patients who were examined for mediastinal LAP but were found to have primary lung malignancy or mediastinal lymph node metastasis of other organ malignancies were excluded. Patients whose EBUS-guided biopsy results were evaluated as reactive LAP and had no additional pathology detected during follow-up were included in the study (Figure 1). According to chest X-ray, the sarcoidosis patients were assessed as stage 1 (hilar LAP) and stage 2 (hilar LAP and parenchymal involvement).

EBUS-guided biopsy procedure

Patients presenting to our outpatient clinic for various reasons who had chest computed tomography demonstrating LAP of 10 mm or larger were evaluated as pathologic LAP and underwent EBUS-guided lymph node biopsy (Olympus BF-UC160F-0L8) performed via oropharyngeal approach. Before the EBUS procedure, all patients gargled with 5 mL of 2% lidocaine (Jetmonal 2%®) and received 3 puffs of lidocaine spray (Vemcaine 10%®) to the posterior pharynx for local anesthesia and were sedated using midazolam (for patients ≤60 years old, initial dose of 2–2.5 mg increasing to total dose of 7.5 mg as needed; for patients >60 years old, initial dose of 0.5–1 mg increasing to total dose of 3.5 mg as needed). Oxygen therapy was initiated as needed.

Calculation of systemic immune inflammatory index (SII)

Pre-biopsy hematologic parameters were determined from blood samples obtained from a peripheral vein at admission to our clinic. Samples were collected in tubes containing ethylenediaminetetraacetic

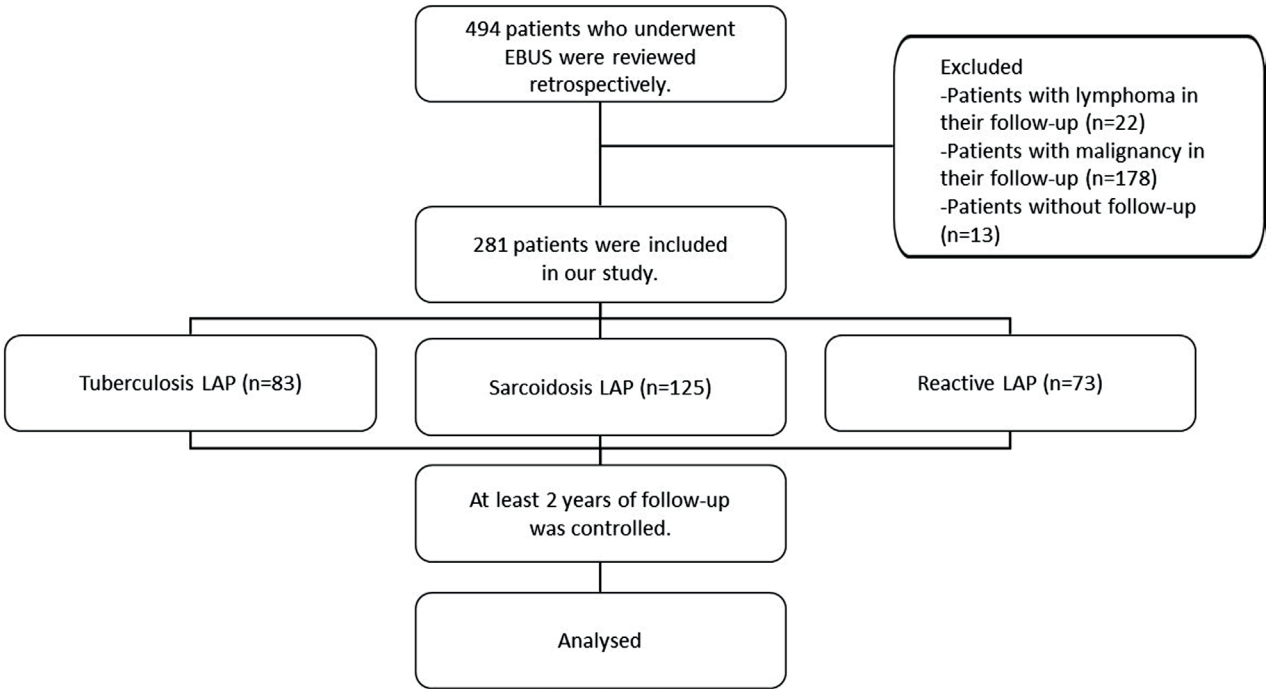

Figure 1. CONSORT diagram.

acid and analyzed by automated blood count according to hospital procedures. An automated hematological analyzer was used to measure hematological parameters (Coulter LH 780 Analyzer, Brea, CA).

The patients' SII values were calculated using the following formula: SII = Platelet count ($\times 10^3/\mu L$) × Neutrophil count ($\times 10^3/\mu L$) / Lymphocyte count ($\times 10^3/\mu L$).

Statistical analysis

Statistical analysis was performed in IBM SPSS Statistics for Windows version 22.0 (IBM Corp., Armonk, NY). Between-group comparisons were performed using Pearson's chi-square test for parametric data and Mann-Whitney U test for non-normally distributed numerical data. Demographic data and laboratory parameters were compared among the groups using the Kruskal-Wallis test, followed by post hoc pairwise comparisons using independent-samples t-test. Pearson correlation analysis was used to evaluate the relationship between laboratory parameters and radiological scores. Receiver operating characteristic (ROC) curve analysis was used to determine whether the continuous variable had diagnostic value, and a cut-off value was determined using Youden index. A p-value less than 0.05 was considered statistically significant.

Results

The mean age of the 281 patients included in our study was 41.4 ± 20.6 years. The mean age was 40.9 ± 16.1 years for patients diagnosed with sarcoidosis, 36.3 ± 18.6 years for those with TB, and 48.1 ± 27.9 years for those with reactive LAP. The difference in mean age between the groups was found to be statistically significant (p=0.04).

Eighty-seven (63%) patients with sarcoidosis, 48 (57.8%) patients with TB, and 11 (15.1%) patients with reactive lymph nodes were women. A statistically significant difference was also observed in the comparison of the groups according to sex (p<0.001).

Comparison of hematologic parameters, erythrocyte sedimentation rate (ESR), and SII values of the groups are shown in Table 1. Lymphocyte count, neutrophil count, platelet count, ESR, and SII differed significantly between the groups (p<0.001,

Table 1. Comparison of hematologic parameters and SII level of the groups.

	Tuberculosis LAP (n=83) Mean ± SD	Sarcoidosis LAP (n=125) Mean ± SD	Reactive LAP (n=73) Mean ± SD	p
Lymphocytes (/μL)	1346.9 ± 580.5[a,b]	1810.3 ± 605.4[b]	2510.1 ± 655.2	<0.001
Neutrophils (/μL)	4910.2 ± 1780.6[b]	5210.6 ± 1921.3[b]	4400.4 ± 1752.6	0.007
Platelets (/μL)	345560.1 ± 173100.1[a,b]	282560.2 ± 98330.5[b]	233502.2 ± 77320.5	<0.001
ESR (mm/h)	27.6 ± 18.9[a,b]	17.2 ± 15[b]	10.1 ± 9.8	<0.001
SII	1434525.3 ± 1004626.7[a,b]	1023430.4 ± 1218086.2[b]	562660.1 ± 770411.1	<0.001

Abbreviations: ESR: Erythrocyte sedimentation rate; SII: Systemic immune-inflammation index; LAP: Lymphadenopathy. Kruskal-Wallis analysis was used to compare among the groups. [a] Significant difference (p<0.05) for tuberculosis LAP vs. sarcoidosis LAP; [b] Significant difference (p<0.05) for tuberculous LAP and sarcoidosis LAP vs. reactive LAP.

Table 2. Comparison of hematologic parameters and SII levels in stage 1 and 2 sarcoidosis patients.

	Stage 1 Sarcoidosis (n=57) Mean ± SD	Stage 2 Sarcoidosis (n=68) Mean ± SD	p
Lymphocytes (/μL)	1960.2 ± 590.7	1503.6 ± 540.6	0.001
Neutrophils (/μL)	4790.4 ± 1614.2	5560.8 ± 2110.1	0.06
Platelets (/μL)	255602 ± 65120.4	310710.3 ± 115370.6	0.009
ESR (mm/h)	11.4 ± 10.1	22.6 ± 16.9	0.001
SII	636345.9 ± 42097.1	1347898.3 ± 1237404.6	0.001

Abbreviations: ESR: Erythrocyte sedimentation rate; SII: Systemic immune-inflammation index.

=0.007, <0.001, <0.001, and <0.001, respectively). In the comparison of SII between groups, it was observed that SII was significantly higher in patients followed up for tuberculous lymphadenitis compared to patients with sarcoidosis and reactive LAP (p=0.01 and <0.001, respectively) and in sarcoidosis patients compared to patients with reactive LAP (p=0.002).

Table 2 shows the hematologic parameters, ESR, and SII values of the patients followed up for sarcoidosis. Platelet count, ESR, and SII were significantly higher in stage 2 sarcoidosis compared to stage 1 sarcoidosis, while lymphocyte count was lower (p=0.009, 0.001, 0.001, and 0.001, respectively).

The ROC curve analysis of SII in patients with granulomatous lymphadenitis associated with TB and sarcoidosis patients versus patients with reactive LAP is shown in Figure 2. The area under the curve (AUC) was 0.807. At a cut-off value of 336.8, the sensitivity and specificity of SII in differentiating granulomatous LAPs from reactive LAPs was 93% and 65%, respectively.

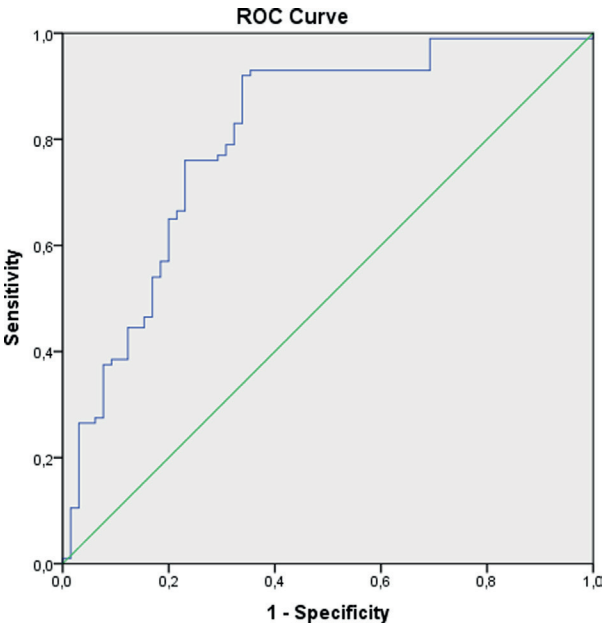

Figure 2. ROC curve analysis of SII for differentiation of granulomatous LAP and reactive LAP.

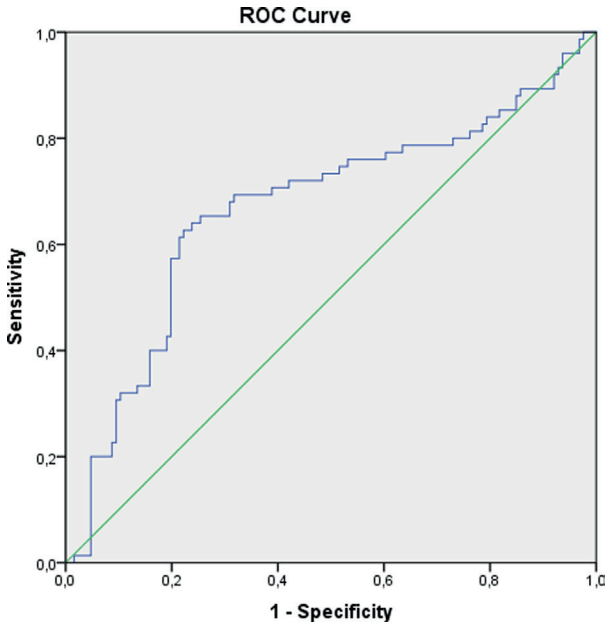

Figure 3. ROC curve analysis of SII in patients with tuberculosis and sarcoidosis LAP.

ROC curve analysis of SII in patients with sarcoidosis and tuberculous LAP is shown in Figure 3. Accordingly, the AUC was 0.668 and the cut-off value for SII was 890.7, with a sensitivity of 70% and specificity of 66% in differentiating tuberculous and sarcoidosis lymphadenitis.

In the correlation analysis, a statistically significant positive correlation was observed between SII and ESR (r=0.63, p=0.01).

Discussion

In our study, we observed that SII levels were higher in patients with TB and sarcoidosis who were followed for granulomatous lymphadenitis compared to patients with reactive LAP. SII levels were also higher in patients with TB as the etiology of LAP compared to those with sarcoidosis. Among LAP patients with sarcoidosis, higher SII was observed in stage 2 patients with parenchymal involvement compared to stage 1 patients. Correlation analysis between SII and ESR revealed a positive correlation.

Regardless of the cause of granulomatous diseases, their pathogenetic mechanisms are similar. Caseification necrosis in TB leads to the formation of tubercles. Macrophages in the granuloma transform into epithelioid cells (11). In sarcoidosis, there is no true caseation necrosis, but small areas of eosinophilic necrosis may be found (12). Subsequently, epithelioid cells disperse with developing fibroblastic connective tissue cells and collagen tissue develops. Some inclusion bodies can be seen in the cytoplasm of giant cells, including Schaumann bodies, asteroid bodies, and centrospheres. In the absence of caseous necrosis in the granulomas, it is morphologically impossible to make a differential diagnosis between TB and sarcoidosis (13).

Many parameters have been used in the differential diagnosis of these two pathophysiologically similar diseases (14). PPD test and hematologic parameters such as serum ACE level, soluble IL-2 receptor level, serum amyloid A, NLR, and PLR have been used (10, 15, 16). However, despite many laboratory parameters, no serologic test or hematologic parameter has enabled a definitive distinction. The fact that serological parameters cannot be obtained quickly from health institutions due to increasing costs has increased the trend towards more economical and easily accessible tests.

Peripheral lymphopenia has been detected in diseases with granulomatous infection such as sarcoidosis and TB (17, 18). Increased lymphocyte density around the granuloma and secondary peripheral lymphopenia have been implicated in the etiology. The reason for this increase is thought to be an imbalance between regulatory and effector T lymphocytes. It has been suggested that the accumulation of regulatory T lymphocytes around the granuloma results in an antiproliferative effect on effector T lymphocytes (19, 20).

In studies on the secondary thrombocytosis that develops in chronic inflammatory diseases including granulomatous diseases, increased levels of platelet-derived growth factor (PDGF) and platelet factor 4 (PF4) have been observed in patients with both TB and sarcoidosis (21). In patients with TB and sarcoidosis, these parameters increased with disease progression and regressed with treatment, especially in patients with TB. These parameters, which increase with increasing platelet levels, led to the investigation of the role of platelets in granulomatous diseases (22). This research has shown that platelets increase around granuloma structures in diseases with pulmonary granulomas and that platelet-leukocyte

interaction may play an important role in the formation of immune response in inflammatory diseases, especially TB (20, 23).

In our study, it was observed that SII levels were higher in patients followed for tuberculous LAP compared to patients followed for sarcoidosis and reactive LAP. In studies conducted in TB patients and sarcoidosis patients, the increase in platelet levels was higher in TB patients than in sarcoidosis patients, which was interpreted in favor of using PLR to differentiate the two diseases. This may be why SII levels were higher in patients with TB than in patients with sarcoidosis and reactive LAP in our study. In addition, platelet-leukocyte interaction, which is increased in TB patients to suppress active infection, may have caused deepening of lymphopenia compared to other groups. This may have caused SII to increase in TB patients.

We also noted that SII level increased in accordance with sarcoidosis stage. The increased inflammation and granuloma number with progressive sarcoidosis stage may have caused an increase in platelet level and deepening of lymphopenia as a result, possibly explaining the higher SII levels with increasing stage as seen in our study. We observed that SII had higher sensitivity and specificity when differentiating patients with granulomatous LAP from patients with reactive LAP than when differentiating between tuberculous and sarcoidosis LAP. This may be attributed to similar changes in hematologic parameters in TB and sarcoidosis patients with granulomatous LAP. The moderately strong positive correlation between SII and ESR in granulomatous diseases with inflammation also suggests that SII may be an inflammatory marker.

A limitation of our study was that Stage 1 and 2 sarcoidosis patients constituted a significant portion of the patients who underwent EBUS-guided lymph node biopsy. As a result, our study was not comprehensive enough to cover other stages of sarcoidosis. In addition, the inability to create age- and sex-matched patient groups was another limitation. However, the changing incidence of granulomatous diseases with age and sex is the main reason for this limitation.

In conclusion, the differential diagnosis of granulomatous diseases is still a challenge for many physicians despite improved techniques. Although studies to facilitate this distinction provide some guidance, they do not enable a definitive diagnosis. SII, a recent parameter of interest in such difficult-to-differentiate diseases, is easily obtained and may be valuable in the differentiation of granulomatous diseases such as TB and sarcoidosis from both reactive LAP and from each other.

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Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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

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