

Elevated neutrophil-to-lymphocyte ratio in the diagnosis of subacute thyroiditis

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Summary. Subacute thyroiditis (SAT) is a self-limiting inflammatory condition of the thyroid gland in which multinucleated giant cells constitute a key histological finding. The neutrophil-lymphocyte ratio (NLR), determined from peripheral blood, is accepted as an available and practical indicator of the systemic inflammation. The purpose of this study was to determine the neutrophil-to-lymphocyte ratio (NLR), a novel marker of inflammation, in patients with SAT and to compare these values with those from healthy subjects. A total of 150 participants were included in the study, 75 SAT patients and 75 healthy volunteers. Retrospectively, demographic and laboratory data of the subjects were obtained from our institution's database. Patients with active infection, diabetes mellitus, malignancy, other chronic inflammatory diseases and hematologic disorders were excluded from the study. Values for complete blood count (CBC) and serum laboratory parameters of SAT patients were the baseline values obtained at the time of SAT diagnosis. Control subjects consisted of healthy volunteers who visited our institution for a routine check-up. A total of 75 subacute thyroiditis patients 54 (72%) were female and 21 (28%) were males and 50 (66.6%) were female and 25 (33.3%) were male and 75 were healthy adults were included. The mean age was 39.95 ± 14.2 , years for patients with SAT and 37.53 ± 13.45 years for the control group. There was no significant difference between the age for groups ($P = 0.13$). NLR levels were found to be 3.56 ± 2.64 in patients with SAT; NLR levels were found to be 1.41 ± 0.9 in the control group. NLR levels were significantly higher in patients with SAT compared to the control group. Our study showed that increased NLR may be useful as an indicator of the presence of SAT, especially in complicated cases. The assessment of neutrophil-lymphocyte ratio in conjunction with radiological and clinical findings will assist in the achievement of an accurate diagnosis. Larger, prospective studies are required to determine its usefulness in assessing diagnostic potential and treatment outcomes in SAT patients.

Key words: Subacute thyroiditis, neutrophil-to-lymphocyte ratio, diagnosis

Introduction

Subacute granulomatous thyroiditis (SGT), also known as De Quervain's thyroiditis, is a self-limiting, inflammatory disease of the thyroid that is believed to be caused by a systemic viral infection (1-7). It was first diagnosed in 1825, and 18 cases were reported as

"thyroiditis acuta simplex" until 1895. This pathology was compiled by the Swiss surgeon De Quarvein in 1904 and 1936 (4). It typically occurs in the area of the gland in mid-aged hyperthyroid women complaining of pain, tenderness, fatigue and mild fever (1,2,5,6,7).

Complete blood count (CBC)-derived parameters and their relation to certain diseases have recent-

ly received attention from researchers. One of these CBC parameters is the neutrophil-to-lymphocyte ratio (NLR). NLR is considered to be a marker of inflammation and, due to its simplicity and low cost, has been studied in many medical conditions. An elevated neutrophil count in a CBC predicts ongoing inflammation and decreased lymphocyte count is considered to be an indicator of poor prognosis, so a combination of these two measures is generally accepted to be predictive of an inflammatory situation (8). NLR reflects both inflammatory burden (by neutrophil count) and regulatory mechanisms (by lymphocyte count) in inflammatory disease (9,10). Studies suggest NLR is associated with occult inflammation in certain conditions (11-15). In this retrospective study, NLR was determined in 75 SAT subjects and investigated the possible association between SAT and NLR by comparing these values to NLR determined in a healthy population.

Since there is a strong association between inflammation and SAT, and between inflammation and NLR, we aimed to compare NLR values of patients with SAT to those of healthy volunteers.

Materials and Methods

Patients

Patients with diagnosis of SAT who were followed up in the endocrinology clinic of our institution were enrolled to present retrospective study. Diagnosis of SAT was established with a combination of relevant history and findings in physical examination that were supported by characteristic findings on ultrasound scan (diffuse enlargement of the gland, decreased echo pattern and diminished thyroid blood in the doppler) and decreased uptake in thyroid scintigraphy. The study protocol was approved by the ethics committee of Dicle University, Faculty of Medicine, Diyarbakir, Turkey. The study was conducted in accordance with the Declaration of Helsinki.

Biochemical Measurements

Fasting venous blood samples were collected in the morning after 8 h of fasting. The assays were performed at the laboratory in Dicle University's

Faculty of Medicine and Firat University's Faculty of Medicine using a biochemical analyzer (ABX Pentra DX 120; HORIBA, Ltd.). Hemograms were determined with an autoanalyzer (Coulter® LH 780 hematology system; Beckman Coulter, Inc.). The blood samples were processed within 30 min after blood collection.

CBC and serum parameters used in this study were the baseline laboratory findings that were recorded in our database at the time of SAT diagnosis. Control subjects consisted of healthy volunteers who visited our institution for a routine check-up. General characteristics and laboratory data of all participants were obtained from the computerized database of our clinics. White blood cell count (WBC), neutrophil count (Neu), lymphocyte count (Lym), hemoglobin (Hb), hematocrit (Htc), mean corpuscular volume (MCV) and platelet count (PLT) were recorded for all participants. NLR was calculated simply dividing the Neu value by the Lym value.

Exclusion Criteria

Patients with cardiovascular disease, hepatic or renal failure, previously detected malignancies, diabetes mellitus, hyperthyroidism, pregnancy, chronic obstructive pulmonary disease, or who were smokers or using anticoagulant-antiplatelet medications were excluded from the study. Hemoglobin <13 g/dL for males and <12 g/dL for females, and white blood cell counts >12,000 cells and <4000 cells were ignored.

Statistical Analysis

All statistical analyses were performed with the SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). The significance of the mean differences between groups was assessed by Student's *t* test. Also, paired *t* test was used for repeated data in the patient group. Data were presented as mean ± standard deviation. Relationships between variables were tested using Pearson's correlation analysis. Receiver operating characteristic (ROC) curve graphics were used in the comparison of sensitivity and specificity. *P* values less than 0.05 were regarded as significant.

Results

Demographic Findings

A total of 75 subacute thyroiditis patients (54%) were female and 21 (28%) were males and 50 (66.6%) were female and 25 (33.3%) were male (Figure 1) and 75 were healthy adults were included. Mean ages of the SAT and control groups were 39.95 ± 14.2 and 37.53 ± 13.45 years, respectively. The difference was not statistically significant ($p > 0.05$). There was no significant difference between the two groups in terms of age and gender ($p > 0.05$). Mean age was 37.56 ± 10.17 years in female patients with subacute thyroiditis and 46.05 ± 15.07 years in male patients (Figure 2).

Laboratory Findings

NLR levels were found to be 3.56 ± 2.64 in patients with SAT; NLR levels were found to be 1.41 ± 0.9 in the control group. NLR levels were sig-

nificantly higher in patients with SAT compared to the control group.

When the laboratory findings of patients with subacute thyroiditis were compared with the control group, the sedimentation value was significantly higher in the patient group (53.9 ± 14.24 , 11.04 ± 6.86 , $p < 0.01$, respectively). C reactive protein value was significantly higher in the diseased group (7.08 ± 5.65 , 0.44 ± 0.38 , $p < 0.01$, respectively). The leucocyte, neutrophil, neutrophil percentage, lymphocyte percentage and platelet counts were significantly higher in the patient group (Table 1).

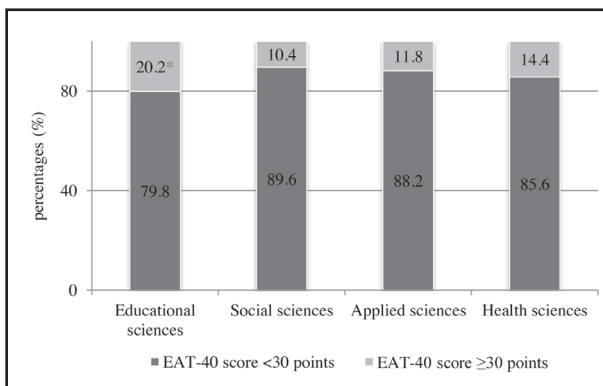


Figure 1. Gender distribution

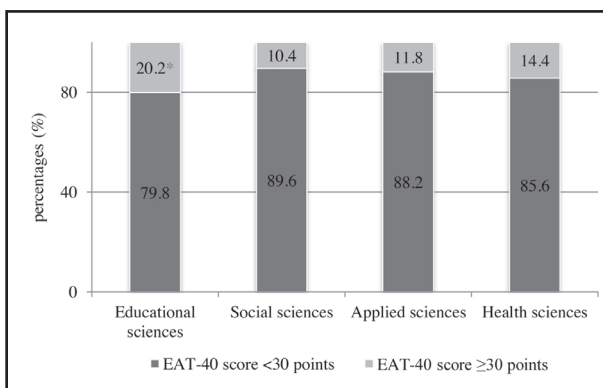


Figure 2. Gender age distribution

Table 1. Laboratory data of the study population.

	SAT group	Control group	P value
ESR (mm/h)	53.9 ± 14.24 n:75	11.04 ± 6.86 n:75	0,001
CRP (mg/L)	7.08 ± 5.65 n:75	0.44 ± 0.38 n:75	0,001
WBC (u/mm^3)	9.94 ± 3.49 n:75	7.92 ± 1.82 n:75	0,002
NEU %	66.9 ± 9.59 n:75	58.8 ± 9.16 n:75	0,001
LYM %	23.64 ± 8.29 n:75	31.11 ± 8.19 n:75	0,001
NEU/LYM	3.56 ± 2.64 n:75	1.41 ± 0.9 n:75	0,001
HEMOGLOBIN	12.12 ± 1.46 n:75	13.81 ± 1.58 n:75	0,001
PLATELET (u/mm^3)	367.63 ± 117.14 n:75	283.37 ± 82.01 n:75	0,001
MPV (fl)	7.81 ± 1.1 n:75	8.78 ± 1.35 n:75	0,001
PDW (fl)	17.77 ± 1.19 n:75	20.19 ± 1.11 n:75	0,001
FT3 (pg/mL)	11.03 ± 5.45 n:75	4.86 ± 0.5 n:75	0,001
FT4 (ng/ml)	42.18 ± 17.67 n:75	16.67 ± 2.53 n:75	0,001
TSH (uIU/mL)	0.03 ± 0.05 n:75	1.6 ± 1.25 n:75	0,001

ESR, Erythrocyte Sedimentation Rate; CRP, C-Reactive Protein; WBC, White Blood Cell; NEU, Neutrophil; LYM, Lymphocyte; MPV, Mean Platelet Volume; PDW, Platelet Distribution Width; FT3, Free T3; FT4, Free T3; TSH, Tiroid Stimulating Hormon

Discussion

The main finding of our study is that NLR was elevated in SAT patients compared with the healthy control subjects. This is the first reported association between SAT and NLR.

NLR is a hematologic parameter that is studied the most. Like other hematological inflammatory markers, most studies focus on its prognostic power (16). Shimada et al. proposed NLR as a reliable predictor of inflammatory burden (17). C-reactive protein (CRP), which responds immediately to infectious or inflammatory stimulus, is one of the most well-established inflammatory markers and, interestingly, NLR was found to correlate with CRP (18,19). There are a number of reports studying NLR in various thyroid diseases. Researchers from Taiwan showed that NLR correlated with the size of thyroid tumors (20). Moreover, elevated NLR was proposed as a negative prognostic factor for survival in subjects with papillary thyroid cancer (21). Aside from thyroid neoplasm, NLR has also been found to correlate with other types of neoplasms (22,23). Inflammation plays a critical role in tumor development, progression, clinical presentation and prognosis of cancer (24). SAT is also characterized by a prominent inflammatory burden, which is consistent with neutrophilic and lymphocytic inflammation of the thyroid gland; (25) therefore, the increased NLR seen in SAT patients compared with controls in this study is likely to be a result of acute inflammation. In our study, when the laboratory findings of patients with subacute thyroiditis were compared with the control group, the sedimentation value was significantly higher in the patient group. C reactive protein value was significantly higher in the diseased group. The leucocyte, neutrophil, neutrophil percentage, lymphocyte percentage and platelet counts were significantly higher in the patient group.

Fair number of Multinucleated Giant Cells, epithelioid cell granulomas, inflammatory cells (lymphocytes, macrophages and neutrophils), degenerated follicular epithelial cells, and a dirty background composed of cellular debris, naked, degenerated nuclei and thick colloid are the key cytological characteristics for the diagnosis of SAT (26). As in our study, potent inflammatory markers such as high-level NLRs give

strong insight into the diagnosis and progression of the SAT.

Elevated NLR has been reported in patients with familial Mediterranean fever (FMF) and has emerged as a valuable predictor of the development of amyloidosis (27). Both thyroid follicular cells and inflammatory cells, involved in HT, are capable of producing cytokines that may exacerbate the autoimmune process and the inflammatory response; (28,29) therefore, mechanisms similar to those seen in FMF may induce elevated NLR.

On gross examination, the thyroids affected by SAT are typically asymmetrically enlarged and firm with a tan-white cut surface and ill-defined nodularity (30). The histological appearance of SAT varies with the phase of the disease. The early phase, which correlates with a hyperthyroid status, is characterized by destruction of follicular epithelial cells with colloid extravasation and colonization of follicles predominantly by neutrophils forming microabscesses. As the disease progresses the acute inflammation is gradually replaced by lymphocytes, histiocytes, and characteristically multinucleated giant cells engulfing colloid. Histologically, the late phase is remarkable for increasing amounts of interfollicular fibrosis and corresponds to hypothyroid phase (30, 31). In our study; In order to increase the value of the study, In the acute phase of the SAT, the cases were taken to study.

In healthy populations, NLR is increased in the elderly; however, the mean age of the 75 SAT patients was not different from the healthy controls in our study so the increase in NLR seen in our study cannot be attributed to this age-related correlation.

Limitations of study; the number of total patient considered in the study were 75, however future studies needs to be undertaken involving more number of cases along with nuclear, hormonal and radiological correlation. The follow up of the patients were also not conducted as it was a retrospective study.

In conclusion, NLR could prove to be an important tool for measuring systemic inflammation in SAT patients since it is cost effective, readily available, and easily calculated. Our study showed that increased NLR may be useful as an indicator of the presence of SAT, especially in complicated cases. The assessment of neutrophil-lymphocyte ratio in conjunction

with radiological and clinical findings will assist in the achievement of an accurate diagnosis. Larger, prospective studies are required to determine its usefulness in assessing diagnostic potential and treatment outcomes in SAT patients.

Acknowledgements

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