Neutrophil to Lymphocyte Ratio is Useful in Differentiation of Malign and Benign Thyroid Nodules

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Objective: Significant amount of thyroid nodules are malignant. Inflammation plays crucial role in the pathogenesis of many disorders, including cancer. Neutrophil to lymphocyte ratio (NLR), has been suggested as an index of inflammatory response and association between increased NLR and cancer has also been reported. In this retrospective analysis, we aimed to study NLR levels in patients with malign and benign thyroid nodules and healthy control subjects.

Methods: The patients who underwent surgery for nodular goiter in general surgery clinics of our university hospital between June 2012 and June 2015 and 68 healthy volunteers were included. Patients with thyroid nodules divided into malign or benign nodule groups according to the pathology report. Thyroid carcinomas other than micropapillary tumor were excluded. Preoperative hemogram parameters of these groups were compared.

Results: Mean NLR of malign nodule group (2.1±0.9%) was significantly higher than both those in benign nodule (1.7±0.9%) and control groups (1.7±0.6%).

Conclusion: We suggest that elevated NLR in patients with thyroid nodules in preoperative period may be an indicator of underlying malign nodular disease. Increased NLR in such patients should encourage physician to perform cancer screening in thyroid gland. [*P R Health Sci J 2019;38:60-63*]

Key words: Neutrophil to lymphocyte ratio, Inflammation, Thyroid nodule, Cancer

Thyroid nodules are one of the most common clinical problems with a prevalence as high as 5% in women and 1% in men in iodine deficient regions (1). The rate of thyroid nodules detected by ultrasound imaging is about 19-68%, especially in women and older subjects (2). Since 7-15% of thyroid nodules are malignant, these nodules should be evaluated for possible malignancy (3, 4).

Inflammation plays a crucial role in the pathogenesis of many disorders. While some diseases, such as rheumatoid arthritis, cause prominent amount of inflammation, some others (e.g. irritable bowel syndrome) cause only a small inflammatory burden. Furthermore, association between inflammation and malignancy is well established (5).

Novel inflammatory markers derived from routine hemogram tests have been frequently studied recently. One of these markers is neutrophil to lymphocyte ratio (NLR), which has been suggested as an index of inflammatory response (6). It is well-known that systemic inflammation stimulates neutrophilia and lypmhopenia, which result in an increase in NLR (7, 8). Increased NLR has been reported in various forms of inflammatory and malignant diseases (9-12).

In the present study, we studied NLR levels of the patients with malignant and benign thyroid nodules retrospectively and compared them with the NLR in healthy subjects.

Material and Methods

The patients whom underwent surgery in general surgery clinics of our university hospital for nodular goiter between June 2012 and June 2015 have been included to the study, after obtaining institutional directorate approval. Patients having thyroid nodules divided into malign nodule or benign nodule groups according to the results of pathological assessment. Healthy volunteers were enrolled form subjects who visited outpatient internal medicine clinics of our institution for a check-up. All the laboratory assays were held in biochemistry laboratory of our institution. Preoperative hemogram values, white blood cell count (WBC), hemoglobin (Hb), hematocrit (Htc), mean corpuscular volume (MCV), platelet count (PLT), neutrophil count (neu) and lymphocyte count (lym) were recorded. The preoperative hemogram test results used

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in comparison. NLR was obtained by simply division of neu to lym value and presented as % (11).

Exclusion criteria were as follows: patients with thyroid carcinoma other than micropapillary tumor, active infection, diabetes mellitus, and any other chronic inflammatory diseases, such as rheumatoid arthritis, malignancy and pregnancy. Patients on chronic aspirin treatment were also excluded from the study. Automatic analyzer of LH 780 model of Beckman Coulter device (Beckman Coulter In.; Bre CA) was used for complete blood count analyses in the laboratory of our institution. As well, other biochemical and pathological assays were conducted in laboratories of our university hospital. Statistical analysis done by SPSS software (SPSS15.0; SPSS Inc., Chicago, IL, USA). Data were expressed as mean ± SD or median (min-max). One way ANOVA test or Kruskal-Wallis test used to compare variables in study population. A p value lower than 0.05 was considered statistically significant.

Results

130 patients with malignant and 109 patients with benign thyroid nodules and 68 healthy subjects were included.

Mean age of malignant nodule, benign nodule and control groups were 44±11, 43±7 and 43±8 years, respectively. Age was not significantly different between groups (p=0.20). 83 of 109 in benign nodule group, 99 of 130 in malign nodule group and 60 of 68 in control group were women. Gender was not statistically different between groups, either (p=0.10).

WBC (p=0.22), Hb (p=0.65), Htc (p=0.22), MCV (p=0.26) and PLT (p=0.68) levels were not statistically different between study groups. Mean neutrophil counts of the study groups were not statistically different (p=0.58), however, mean lymphocyte count in malignant thyroid nodule group was significantly lower than benign nodule and control groups in our study (p=0.001).

Mean NLR of malign nodule group (2.1±0.9) was higher than both those in benign nodule (1.7±0.9) and control groups (1.7±0.6). The difference between groups was statistically significant (p=0.002).

General characteristics and laboratory data of the study population were summarized in table 1.

Table 1. General characteristics and laboratory data of the study groups

	Groups			p
	Malignant Thyroid nodule	Benign Thyroid nodule	Control	
Gender				
Men (n)	31	26	8	0.10
Women (n)	99	83	60	
	Mean ± SD			
Age (years)	44 ±11	43 ± 7	43 ± 8	0.20
WBC (k/mm^3)	6.9 ± 1.6	7.2 ±1.9	7.2 ±1.5	0.22
MCV (fL)	85 ± 4	87 ± 4	86 ± 4	0.26
PLT (k/mm^3)	256 ± 66	259 ± 59	264 ± 49	0.68
NLR	2.1 ± 0.9	1.7 ± 0.9	1.7 ±0.6	0.002
Neutrophil count (k/mm^3)	4.1 ± 1.4	3.92 ± 1.26	3.96 ± 1.12	0.58
Lymphocyte count (k/mm^3)	2.13 ± 0.6	2.41 ± 0.7	2.44 ± 0.6	0.001
	Median (min-max)			
Hb (g/dl)	13.4 (11-18)	13.5 (12-16)	13.7 (12-18)	0.65
Htc (%)	40 (31-50)	41 (35-47)	40.5 (36-51)	0.22
TSH (uIU/ml)	1.3 (0.1-5.7)	1 (0.1-4.4)	1.5 (0.3-4)	0.01
FT3 (pg/ml)	2.9 (0.4-6)	3.3 (2.2-5.4)	3.3 (2.3-4.5)	<0.001
FT4 (ng/dl)	1.2 (0.7-4.2)	1.1 (0.7-1.7)	1.1 (0.7-1.7)	<0.001

TSH: Thyroid stimulant hormone, FT3: Free T3, FT4: Free T4

Discussion

The main finding of the present study is that patients with malign thyroid nodules are associated with greater NLR compared to patients with benign nodules and healthy subjects.

Association between cancer and inflammation has been well-established (13). Markers of acute inflammatory phase response have been introduced as sensitive and reliable markers of inflammatory burden in malign diseases (14) and clinicians have developed prognostic scoring systems based on these markers (15).

Data in literature suggest that NLR was an inflammatory marker and, as a novel inflammatory indice, it may have relevance with cancer, too. Systemic inflammation has been associated with neutrophilia and lymphocytopenia, thus, elevated NLR value (6, 16). Therefore, NLR may be a new inflammatory marker. In our study, although neutrophil counts of the study groups were similar, lymphocyte count was significantly lower in malignant thyroid nodule group than benign nodule and control groups resulting in elevated NLR.

Association between NLR and cancer is an issue of interest in recent years. For example, increased pretreatment NLR values in ovarian cancer suggested to have predictive value for survival in these patients (10). NLR has prognostic value in other certain types of neoplasms (14, 17-20). In colorectal cancers, besides its independent prognostic value, NLR has been reported to be associated with survival (21). Tumor stage has been reported to be related with elevated NLR in a study from Japan in gastro-esophageal cancers (22). Poor prognostic factors (weight loss, reduced functional capacity, poor performance status) in pancreatic cancer patients were also associated with increased NLR values (23). Gomez et al claimed that elevated NLR was associated with not only survival, but also tumor invasion and occurrence of nodal disease and satellite lesions in hepatocellular carcinoma (24). NLR had also predictive value in estimating survival in patients with lung cancer (25). Thyroid cancer should not be free of such association with NLR.

Besides other types of cancer, NLR has also been found to be associated with thyroid malignancies. In a pilot study, increased NLR was reported in subjects with papillary thyroid cancer (26). In contrast to our findings, Kim et al reported

that NLR was elevated in patients with either benign or malignant thyroid nodules (27). However, they have studied advanced papillary thyroid carcinomas whereas we have studied micropapillary carcinoma patients. Nevertheless, tumor size was reported to be correlated with NLR in patients with thyroid cancer (28).

Underlying mechanisms for increased NLR in cancer patients is not clear. Chronic inflammation induce neoplastic growth, however, malignancy itself may also stimulate chronic inflammation and production of inflammatory markers (14). Inflammatory cytokines which released by inflammatory cells after stimulus may interact with neutrophil and lymphocyte production in bone marrow. Chung et al reported that lymphocytopenia was associated with elevated interleukin levels in patients with sepsis (29). Inflammatory stimuli cause increased IL-6 and elevated neutrophil count in animal models (30). In some cancer studies elevated NLR has been associated with increased interleukin levels (31, 32). Therefore, reduced lymphocyte and increased neutrophil count might be responsible of elevated NLR. However, in our study, lymphocyte count was reduced but neutrophil count was not elevated in patients with malignant nodules.

Another explanation of increased NLR in malign thyroid nodules should be that lymphocytes were involved in tumor micro-environment (13). Involvement and utilization of lymphocyte population in tumor may cause a gradual decrease in lymphocyte count which result in an increase in NLR. Nevertheless, NLRs of study groups were statistically different in our report.

Elevated NLR has been reported in other thyroid issues, also. Keskin et al found that NLR was increased in euthyroid patients with chronic autoimmune thyreotidis (33). In another study, authors reported higher NLR values in subjects with Hashimoto's disease (12). Autoimmune markers of thyroid diseases were not studied in present report, which could be a limitation.

In this report, we have found that NLR levels in benign thyroid nodule group were similar to those in healthy volunteers. Malignancy may induce sufficient amount of inflammatory stimuli to cause NLR elevation, but, thyroid nodule alone may not be able to cause enough inflammatory burden. Similarly, Seretis et al reported that NLR of patients with benign goiter was not statistically different from healthy controls (26).

The retrospective design and relatively small study population are two main limitations of our study which make our results difficult for interpretation. Another limitation is lack of thyroid sonography findings in control subjects and incomplete data about antithyroidal autoantibodies due to the retrospective observation.

In conclusion, we suggest that elevated NLR in patients with thyroid nodules in preoperative period may be an indicator of underlying malign nodular disease. Increased NLR in such patients should encourage physician to perform cancer screening in thyroid gland.

Resumen

Objetivos: Los nódulos tiroideos son uno de los problemas clínicos más comunes en todo el mundo con una prevalencia de hasta el 5% y el 1% en mujeres y hombres, respectivamente. Una cantidad significativa de estos nódulos son malignos. La inflamación juega un papel crucial en la patogénesis de muchos trastornos, incluido el cáncer. Se ha sugerido la relación de neutrófilos a linfocitos (NLR) como un índice de respuesta inflamatoria y los autores encontraron una asociación entre el NLR aumentado y el cáncer. En el presente análisis retrospectivo, nuestro objetivo fue estudiar los niveles de NLR de los pacientes con nódulos tiroideos malignos y benignos y compararlos con los NLR en sujetos sanos. Métodos: Los pacientes fueron sometidos a cirugía en las clínicas de cirugía general de nuestro hospital universitario para el bocio nodular entre 2012 y 2015 se incluyeron en el estudio. Los pacientes con nódulos tiroideos divididos en dos grupos según la patología informan grupo de nódulos malignos o grupo de nódulos benignos. Se compararon los parámetros del hemograma de estos grupos. Resultados: La media de NLR del grupo de nódulos malignos (2.1±0.9) fue significativamente mayor que los niveles de nódulos benignos (1.7 ± 0.9) y control (1.7 ± 0.6). Conclusión: Sugerimos que un NLR elevado en pacientes con nódulos tiroideos en el período preoperatorio puede ser un indicador de enfermedad nodular maligna subyacente. El aumento de NLR en tales pacientes debería alentar al médico a realizar exámenes de detección del cáncer en la glándula tiroides.

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