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Research Article

Predictive value of inflammatory cell ratios in incidental thyroid papillary carcinoma

İnsidental tiroid papiller karsinomda inflamatuvar hücre oranlarının prediktif değeri

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ABSTRACT

Introduction: Due to the well-known relationship between inflammatory processes and carcinogenesis, the diagnostic and prognostic value of systemic inflammatory markers are at the focus of research. This study aimed to investigate the predictive value of inflammatory cell data obtained from complete blood count in incidentally detected thyroid papillary carcinoma.

Methods: A total of 100 cases were included in the study, consisting of histopathologically diagnosed multinodular hyperplasia (MNH) (N = 20), lymphocytic thyroiditis (LT) (n = 20), incidental thyroid papillary carcinoma (ITPC) (n = 20), incidental papillary carcinoma and lymphocytic thyroiditis (ITPCLT) (n = 20), and thyroid papillary carcinoma (TPC) (n = 20). Neutrophil / lymphocyte ratio (NLR), platelet/ lymphocyte ratio (PLR), platelet/neutrophil ratio (PNR), lymphocyte/ monocyte ratio (LMR) and lymphocyte/ eosinophil ratio (LER) values were compared between the groups.

Results: No significant difference was detected between the groups concerning the mean inflammatory cell and platelet values. However, statistical significance was observed between the ITPC and ITPCLT groups regarding the mean LMR and LER values (p=0.009 and p=0.037, respectively). Higher LMR was found in the ITPC group, while higher LER was seen in the ITPCLT group.

Conclusions: We suggest that besides ratios such as NLR and PLR used as systemic inflammatory markers in carcinogenetic processes, the evaluation of LER and LMR might be imperative as well. Therefore, these potential markers should be studied in bigger series of tumors, especially where inflammatory processes are involved in the etiology.

Keywords: Thyroid cancer, papillary carcinoma, lymphocytes, eosinophils, monocytes, neutrophils

ÖZ

Giriş: İnflamatuvar süreçlerin karsinogenetik süreçler ile ilişkisi bilinmekte ve sistemik inflamatuvar belirteçlerin tanısal ve prognostik değeri araştırılmaktadır. Bu çalışmada insidental olarak saptanan tiroid papiller karsinomlarda tam kan sayımından elde edilen inflamatuvar hücre verilerinin prediktif değerini araştırmak amaçlanmıştır.

Yöntem: Histopatolojik tanıları multinodüler hiperplazi (MNH) (n=20), lenfositik tiroidit (LT) (n=20), insidental tiroid papiller karsinom (İTPK) (n=20), insidental papiller karsinom ve lenfositik tiroidit (İTPKLT) (n=20) ve tiroid papiller karsinom (TPK) (n=20) olmak üzere toplam 100 olgu çalışmaya dahil edildi. Olguların nötrofil/ lenfosit oranı (NLO), platelet lenfosit oranı (PLO), platelet/ nötrofil oranı (PNO), lenfosit monosit oranı (LMO) ve lenfosit eozinofil oranı (LEO) değerleri gruplar arasında karşılaştırıldı.

Bulgular: İnflamatuvar hücre ortalamaları ve platelet verileri incelendiğinde gruplar arasında bariz farklılık dikkati çekmedi. İnsidental tiroid papiller karsinom ile yapılan analizlerde İTPKLT grubu ile arasında LMO ve LEO açısından belirgin istatistiksel anlamlılık gözlendi (p değerleri sırası ile 0,009 ve 0,037). Buna göre LMO İTPK'da yüksek, LEO ise İTPKLT grubunda yüksek saptandı.

Sonuç: İnflamatuvar hücrelere dair karsinogenetik süreçlerde salt sistemik inflamatuvar belirteçler olarak kullanılan NLR, PLR gibi oranların değil LEO ve LMO gibi oranlarında değerlendirilmesinin gelecekte önem arz edebileceğini ve bu nedenle özellikle inflamatuvar süreçlerin etyolojide yer aldığı tümörlerde geniş olgu serilerinde incelenmesi gerektiğini düşünmekteyiz.

Anahtar kelimeler: Tiroid kanseri, papiller karsinom, lenfosit, eozinofil, monosit, nötrofil

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Introduction

Thyroidectomy is currently applied in the treatment of many benign and malignant thyroid diseases. Diagnostic methods such as ultrasonography (USG), Doppler examination, scintigraphy, and/or fine-needle aspiration cytology (FNAC) are applied before the operation. Among the benign disease of the thyroid, nodular and multinodular hyperplasia account for the most common diseases, followed by inflammatory diseases of the thyroid (especially lymphocytic thyroiditis), while thyroid papillary carcinoma ranks first among the malignant conditions.

All thyroid malignancies can be diagnosed preoperatively by imaging methods and/or cytological examination, as well as by histopathological studies of the surgical resection materials. These tumors are usually not included in the differential diagnosis; hence, they are called "incidental thyroid carcinoma" that is incidentally detected in the operation material. Their frequency is reported as ranging from 5.7 to 59.0% [1-4] around the world, and from 4.6 to 18.9% [5-7] in Turkey.

Today, complete blood count is a cost-effective test that is easy to access and apply. Among the complete blood count-data, the overall rates of inflammatory cells and their ratios with each other and with platelets are currently studied for many diseases [8]. The involvement of inflammation (in particular in carcinogenetic mechanisms) has led to the investigation of inflammatory cell rates in various tumors [9 911]. In the studies done on thyroid papillary carcinoma, data obtained from complete blood counts such as NLR, PLR, and MPV have been evaluated from various perspectives in the literature. There are reports on the association of elevated NLR and PLR with poor prognosis [12], the relationship between high MPV [13] and elevated NLR [14] with TPC, as well as preoperative elevated NLR and lymph node metastasis and larger tumor size [15]. In this study, the value of complete blood count data for predicting preoperatively undetected incidental papillary thyroid carcinoma was investigated.

Methods

After approval of the ethics committee of Kafkas University Faculty of Medicine (date: 27.09.2017, session number: 2017/08, decision ID: 24), 100 patients who had undergone thyroidectomy at the Kafkas University Medical Faculty Health Research and Application Hospital between 2014 and 2017, with histopathological diagnoses of multinodular hyperplasia (MNH) (n = 20), lymphocytic thyroiditis (LT) (n = 20), incidental thyroid papillary carcinoma (ITPC) (n = 20), incidental papillary carcinoma and lymphocytic thyroiditis (ITPCLT) = 20), and thyroid papillary carcinoma (TPC) (n = 20) were included in the study. Since the combined presence of thyroid papillary carcinoma and lymphocytic thyroiditis were reported to have a favorable prognosis, a separate group was formed as ITPCLT [16]. Patients with comorbidities were excluded from the study. Patients with missing pathological and/or radiological examination results were excluded as well. The pathology preparations and radiological examinations were reviewed by relevant experts regarding missing data.

Complete blood count data examined on the day of operation or the previous day were used in the study. Data generated by an autoanalyzer (ABX PEntra 120, HORIBA, France) were extracted from the hospital automation system. White blood cell count (WBC), neutrophil count (N), lymphocyte count (L), platelet count (P), platelet distribution width (PDW), monocyte count (M), and eosinophil count (E) were obtained from the complete blood count report. Neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), platelet/neutrophil ratio (PNR), lymphocyte/monocyte ratio (LMR), and lymphocyte/eosinophil ratio (LER) were calculated from these data. The Mann Whitney-U test was used for statistical analysis with the SPSS version 15.0 package program (SPSS Inc., Chicago, IL, USA).

Results

The mean age of the patients was 48.9±12.7 years (median 49.5); 86 (86%) were female, and 14 (14%) were male. The mean age and sex distribution of the cases according to the histopathological diagnosis groups are given in Table 1. The mean values of the examined complete blood count data according to the histopathological diagnosis groups are presented in Table 2.

When the mean inflammatory cell and platelet data were examined, no significant difference was observed between the groups. The Mann Whitney-U test showed a statistically significant difference in the monocyte count of the MNH group compared to the LT and ITPCLT groups ($p < 0.001$ and $p=0.002$, respectively), and a decrease to close to statistical significance compared to the TPC group ($p=0.066$). Similarly, the mean eosinophil values were significantly higher in the ITPCLT group compared to the MNH group ($p=0.031$). Although this significant increase was not fully reflected, it was observed that it also affected the LMR and LER (p-values, 0.060 and 0.070, respectively). The PDW values were significant in the multinodular hyperplasia group ($p=0.017$). However, there was no statistical significance in the analysis of other parameters of the multinodular hyperplasia group. Similarly, no statistically significant difference was observed in the comparisons with the LT group, but it was noted that the difference in the mean monocyte levels between the LT and TPC groups were close to significance ($p=0.074$).

There was a significant difference concerning the LMR and LER values between the incidental thyroid papillary carcinoma and ITPCLT groups (p-values, 0.009 and 0.037, respectively). Accordingly, LMR was higher in the ITPC group, while LER was higher in the ITPCLT group.
In cases with combined incidental thyroid papillary carcinoma and lymphocytic thyroiditis, the eosinophil counts were significantly different compared to the TPC group ($p=0.017$), while the monocyte counts and PDW were close to statistical significance (p-values 0.082 and 0.062, respectively).

Table 1. Mean age and gender distribution of cases according to the histopathological diagnosis groups

Histopathological diagnosis group	Mean age SD	Sex, n (%)
Multinodular hyperplasia	46.7±14.7	F= 17 (85) M= 3 (15)
Lymphocytic thyroiditis	50.2±13.8	F= 19 (95) M= 1 (5)
Incidental thyroid papillary carcinoma	47.0±10.5	F= 14 (70) M= 6 (30)
Incidental thyroid papillary carcinoma and lymphocytic thyroiditis	47.5±11.6	F= 18 (90) M= 2 (10)
Thyroid papillary carcinoma	53.3±12.3	F= 18 (90) M= 2 (10)

(SD: Standard deviation, F: Female, M: Male)

Table 2. Mean complete blood count data according to the histopathological diagnosis groups, mean±SD

Inflammatory cell	MNH	LT	ITPC	ITPCLT	TPC
White blood cell count	6.8±2.0	6.9±2.3	7.2±1.9	6.8±1.3	7.4±2.9
Neutrophil count	4.4±1.9	4.6±2.1	4.6±1.8	4.1±1.0	4.9±2.9
Lymphocyte count	1.9±0.6	1.9±0.6	2.0±0.7	2.1±0.5	1.9±0.4
Monocyte count	0.3±0.0	0.4±0.2	0.3±0.2	0.3±0.1	0.3±0.1
Eosinophil count	0.2±0.2	0.2±0.1	0.2±0.1	0.2±0.0	0.2±0.1
Platelet count	270.2±90.7	277.9±63.4	271.6±69.3	265.3±41.9	266.2±105.1
Platelet distribution width	12.5±2.9	13.5±2.2	13.3±2.5	14.5±2.5	12.0±3.1
Neutrophil/lymphocyte ratio	2.6±1.7	2.8±2.2	2.6±1.8	2.0±0.5	2.8±2.8
Lymphocyte/monocyte ratio	2.9±1.6	1.9±1.2	2.3±1.2	1.3±0.4	4.1±9.9
Lymphocyte/eosinophil ratio	127.8±142.0	107.4±54.4	95.2±85.6	101.0±28.8	82.8±44.0
Platelet/lymphocyte ratio	158.4±69.8	167.8±86.3	49.3±62.2	130.0±35.4	147.1±74.0
Platelet/neutrophil ratio	66.6±26.3	69.6±25.0	66.8±30.4	67.3±20.2	64.2±33.7

SD: Standard deviation MNH: Multinodular hyperplasia, LT: Lymphocytic thyroiditis, ITPC: Incidental thyroid papillary carcinoma, ITPCLT: Incidental thyroid papillary carcinoma and lymphocytic thyroiditis, TPC: Thyroid papillary carcinoma

Discussion

More and more studies are showing that inflammation has an impact on the development and prognosis of many tumors [17], and even so markers which are indicators of systemic inflammatory response, may be independent prognostic factors [18]. C-reactive protein, NLR, and PLR values have been reported in studies on a large number of organs and systems, ranging from neoplastic lesions, which have a one-to-one relationship with inflammatory processes [9], to conditions where inflammation is less pronounced [10].

When it comes to the thyroid; Seretis et al. reported in 2013 that NLR was significantly higher in incidental papillary carcinoma than benign nodular goiter [19]. In a study of 161 TPC patients, Gong W et al. reported that preoperative NLR was associated with lymph node metastasis, larger tumor diameter, and multifocality [15]. Similarly, Liu et al. found that increased NLR was encountered in bigger tumors [20]. In a study of prognostic evaluation of NLR, Kim et al. reported increased NLR as a negative prognostic indicator for disease-free survival [21]. In 2017, Özmen et al. reported that increased NLR and PLR levels were associated with high thyroglobulin, and, hence, poor prognosis [12].

In the study of Machairas et al., published in 2017 on 89 TPC and 139 MNH cases, complete blood count parameters were not statistically significant regarding lymphovascular invasion, which is associated with poor prognosis [22]. However, in the same study, PNR was reported to be increased in patients with an extrathyroidal extension (which is among the poor prognostic markers) and in tumors with high pathological stage [22]. In our study; PNR did not show statistical significance between the groups. We consider that this difference is related to the number of cases and group diversity.

In the Kocer et al.'s study, which included inflammatory processes concerning the thyroid in 232 patients, NLR was significantly higher in patients with combined lymphocytic thyroiditis and TPC as well as pure TPC, compared to patients with lymphocytic thyroiditis and multinodular hyperplasia [14]. In our study, we investigated inflammatory cases as pure inflammation and inflammation with incidental papillary carcinoma, and we did not observe statistical significance concerning NLR and PLR between these groups and other groups. Similar to our study, Yaylacı et al. reported that NLR did not differ between the control and papillary carcinoma groups [23].

Unlike the current literature, in our study, it was noted that the number of monocytes among the evaluated complete blood count parameters was significantly higher in the inflammation groups. Compared to the multinodular hyperplasia group, the high level of monocyte mean values close to statistical significance in the TPC group supports the role of inflammatory processes in TPC. In the analysis of incidental thyroid papillary carcinoma groups, it was observed that LER (p=0.037) and LMR (p=0.009) were significantly higher in the ITPCLT group. Hence, we consider that eosinophils are lower in ITPC with concurrent inflammation, and monocytes are lower in pure ITPC. Therefore, eosinophil-monocytes may be markers that deserve investigation for the use in ITPC.

Limitations

In this study, the rate of inflammatory cells was not evaluated in the thyroidectomy materials. Additionally, we had a relatively low sample size, and there was a female dominance, potentially leading to sex difference concerning the complete blood count levels. A sample with a balanced sex distribution could yield more reliable results.

Conclusion

In our study, we evaluated the rate of inflammatory cells using cheap and easily accessible complete blood count data for the incidental detection of thyroid papillary carcinoma, which is increasing in frequency. Contrary to the literature, we found that the complete blood count has limited use in papillary carcinomas. Moreover, we think that in the carcinogenetic processes of inflammatory cells, rather than only measuring the NLR and PLR ratios, which are used only as systemic inflammatory markers, also LER and LMR might become essential in the future. Therefore, these potential markers should be examined in large case series, especially in tumors with inflammatory processes. Finally, we recommend conducting studies with balanced sex distributions to prevent the influence of sex on the blood count results.

Conflict of interest: The authors have no conflict of interest.

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