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Expression of vascular endothelial growth factor in follicular cell-derived lesions of the thyroid: Is NIFTP benign or precancerous?

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ABSTRACT

Objective: Vascular endothelial growth factor (VEGF) is an angiogenic factor that plays an important role in physiological and pathological angiogenesis of the thyroid. The aim of the current study was to determine the expression characteristics of VEGF in follicular cell-derived lesions of the thyroid and to assess whether a new entity noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) is precancerous.

Material and Methods: Patients diagnosed with 33 follicular adenomas (FA), 41 invasive follicular variant papillary thyroid cancer (IN-FVPTC), and 40 NIFTP in surgical resection materials were evaluated retrospectively. Immunostaining was performed on 5-µm paraffin tissue sections. The percentages of immunostaing for VEGF were evaluated on pathological materials. We used a percentage of labeled thyrocytes score (0, no labeling; 1, <30%; 2, 31-60%; 3, >60%) and an intensity score (0, no staining; 1, weak; 2, intermediate; 3, strong). The sum of two scores were accepted as the total score.

Results: Mean ages of the FA, IN-FVPTC, and NIFTP groups were 44.7 ± 11.7 years, 46.9 ± 13.6 years, 43.2 ± 15.4 years, respectively and the mean VEGF immunostaining scores were 44.7 ± 29.3, 50.2 ± 32.54, 4 ± 26.3 respectively. Although there was no statistically significant difference (p= 0.347), the total score of the NIFTPs was higher than the scores of the FA (mean= 3.9 ± 1.8) and IN-FVPTC(mean= 4.3 ± 1.9) groups with a mean value of 4.6 ± 1.7. This result was remarkable. There was no statistically significant difference between tumor diameters and staining percentages (p= 0.750).

Conclusion: Even if there were no statistical differences for VEGF immunostaining, it was high in NIFTPs. Since we know the role of VEGF in tumorigenesis, we can hypothesize that NIPTP can be precancerous. Our argue should be corroborated by a large prospective study.

Keywords: VEGF, NIFTP, thyroid follicular lesions

INTRODUCTION

Thyroid neoplasms have different histological types and biological behaviors. Follicular adenoma (FA) and the follicular variant of papillary thyroid carcinoma (FVPTC) are follicular cell-derived lesions of the thyroid. Pathologic interpretation and definition of these lesions vary with increasing clinical experience, resulting in a decrease in the diagnosis of follicular adenoma while an increase is seen in the diagnosis of FVPTC (1). Noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP) has recently become the main topic of conversation among these lesions. A follicular adenoma is a benign and mostly solitary tumor of the thyroid. Its incidence is 3-4.3% in autopsy series. It is a well-demarcated, encapsulated monoclonal lesion and does not display nuclear changes specific to invasion or papillary thyroid cancer (PTC) like follicular cancer (2). However, it is not exactly known whether some follicular nodules defined as adenomas will be precancerous. It has been shown that some of these lesions can undergo clonal proliferation and carry molecular changes in follicular cell-derived cancers (2). Moreover, a large number of aneuploid cells have been identified in these lesions. In light of this information, there is still an ongoing debate on whether follicular adenoma may be precancerous (2,3). FVPTC is the second most prevalent subtype of PTC, accounting for 10-25% of papillary thyroid carcinomas. According to Tallini's latest update, FVPTC is classified into three subtypes:

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1. Infiltrative (non-encapsulated) FVPTC: Infiltrative tumor with partial or absent tumor capsule. It is similar to classical PTC with its focal papillary structure and extrathyroidal extension and lymph node metastasis (LNM).

2. Non-invasive encapsulated follicular variant of PTC: It is well-demarcated, partially or completely encapsulated, non-invasive, indolent and carries RAS mutation.

3. Invasive encapsulated FVPTC (IN-FVPTC): It has features of capsular, vascular, intrathyroidal invasion. It can metastasize via hematogenous route and carries RAS mutation (4). Of these, noninvasive encapsulated FVPTC has a very good clinic course and prognosis. Nikiforov et al. have evaluated this remarkable feature by retrospectively reviewing 109 patients. While there was no recurrence, metastasis or death in the follow-up of these cases, they were seen in a small number of patients with invasive FVPTC. As a result of the analysis based on their own results and literature data, they have proposed the use of the name 'noninvasive follicular thyroid neoplasm with papillary-like nuclear features' instead of noninvasive encapsulated FVPTC. They have emphasized that the disappearance of the term 'cancer' would thus have clinically and psychologically positive consequences (5,6). However, the definition of 'less than 1% papillae' criterion was changed to 'no well-formed papillae' in 2018 upon need (7). Angiogenesis is effective in many physiological processes and plays a role in pathological conditions such as wound healing, tumor development, and inflammation. Many molecules such as growth factors, cytokines, prostaglandins are among the angiogenic factors. Vascular endothelial growth factor (VEGF) is an angiogenic factor that has a potent effect on angiogenesis. VEGF is a 45kD glycoprotein from the platelet-derived growth factor (PDGF) family, which is secreted from many cells. It was first described as a vascular permeability factor by Senger in 1983 (8,9). VEGF induces and increases angiogenesis/vasculogenesis, vascular permeability, endothelial cell (EC) proliferation, migration, and adhesion of leukocytes. Angiogenesis plays a central role in the development and function of thyroid follicular cells, and in the pathogenesis of benign and malignant diseases of the thyroid (10). Thyroid cancer cells have high mitotic activities and intensely contain VEGF mRNA and protein (11,12). During the malignant transformation process, events such as hypoxia and Ras-activated signal transduction pathway have been shown to regulate VEGF expression (13). Hypoxia is one of the most effective stimuli that initiate angiogenesis by inducing the production of VEGF and its receptors. The expression of VEGF increases in the hypoxic tumoral environment and neovascularization develops (14). The VEGF family consists of A, B, C, D, E forms (15). Of these, VEGF-A is one of the most potent growth factors. It plays a role in physiological vascular growth and pathological angiogenesis, and also modulates tumor proliferation and metastasis process (16,17). There are a few studies that assess the importance of VEGF in only papillary thyroid cancer. As to the best of our knowledge, there are no other studies that compare VEGF immunostaining features of other lesions originating from follicular cells. There isn't any other study evaluating the features of VEGF in NIFTP specifically, whose pathologic significance is unclear. Our study is unique in this regard. We presented VEGF immunostaining features of lesions originating from follicular lesions like follicular adenoma, IN-FVPTC and NIFTP. For this purpose, we used VEGF A, which is a potent stimulant of angiogenesis. We aimed to establish the position of NIFTP regarding these VEGF expression features among these lesions.

MATERIAL and METHODS

A total of 114 consecutive patients who underwent thyroid surgery in our thyroid clinic between December 2016 and June 2020 were retrospectively evaluated. The patients were operated by the same thyroid surgery team. All preparations were evaluated by two experienced pathologists using the diagnostic criteria of WHO Classification (4th edition) (18). According to this classification; encapsulated, non-invasive neoplasms consisting of thyroid follicular cells that do not contain the nuclear features of papillary thyroid carcinoma were diagnosed as follicular adenoma. The diagnosis of NIFTP was based on the revised criteria (7). Primary criteria;

1. Encapulation or clear demarcation,
2. Follicular growth pattern with all of the following no well-formed papillae, no psammoma bodies, <30% solid, trabecular, or insular growth pattern,
3. Nuclear features of papillary carcinoma (i.e. nuclear score of 2-3),
4. No lympho-vascular or capsular invasion,
5. No tumor necrosis or high mitotic activity (<3 mitoses per 10 high-power fields). Secondary criteria;

1. Lack of BRAFV600E mutation detected by molecular assays or immunohistochemistry

2. Lack of BRAFV600E-like mutations or other high-risk mutations (TERT, TP53). Molecular studies were not performed on any of the cases. The tumor which was consisted of follicular structures containing nuclear features of papillary carcinoma but showed infiltration or invasion was diagnosed as follicular variant papillary carcinoma.

Immunohistochemistry (IHC): Formalin-fixed-paraffin-embedded tissue blocks of the cases were sectioned into 3 µm and placed at positively charged slides. After deparaffinization, antigen retrieval was performed. VEGF (Clone VG1, Thermo Fisher Scientific, Fremont, USA) antibody was studied on the Ventana staining platform automated with the Ventana Benchmark Ultra OptiView Universal DAB kit (Ventana Medical Systems, Inc, Tuscon, Ariz). All steps were done using standard and validat-

ed immunohistochemical protocols. Positive control was used for each preparation. All slides were analyzed and evaluated the percentage of immunostaining. They were analyzed under a microscope (Olympus CX41) with 400× magnifications and scored using a semi-quantitative scoring based on the proportion score. The proportion score is the estimation of the proportion of the positive cells within the tissue on the entire slide. The VEGF immunoreactivity was always confined to the cytoplasm of epithelial cells.When interpreting VEGF immunostaining, we modified the assessments used in previous studies (11). We evaluated the immunohistochemical staining of VEGF in thyrocytes using two different scorings. In the first one, the staining intensity score was ranked as 0: no staining; 1: weak; 2: intermediate; 3: strong, and in the other was percentage of labeled thyrocytes score, as 1= <%30; 2: 30-60%; 3: >60%. We used the sum of these as the total score, ranging from 0-6.

This study was conducted in accordance with the Declaration of Helsinki. Ethics Committee Approval was obtained for this study (Acıbadem University, Faculty of Medicine's Ethics Committee; 31.12.2020/Report no: 2020-27/06)

Statistical Analysis

Statistical analysis was performed using SPSS. Continuous data were expressed as mean ± SD, and categorical variables were expressed as percentages. Mann-Whitney U test was used to compare the nonparametric data of the two groups. Relationships among the categorical variables were investigated by the Chi-square test. Spearman's correlation tests were used to measure the degree of association between variables. P values less than 0.05 were considered as statistically significant.

RESULTS

We evaluated 33 follicular adenomas, 41 IN-FVPTC, and 40 NIFTP thyroidectomy specimens. Mean ages of the FA group, IN-FVPTC group, and NIFTP group were 44.7 ± 11.7 years, 46.9 ± 13.6 years, and 43.2 ± 15.4 years, respectively, and similar among the groups. Sex (female to male) distributions were 25/8, 29/12, and 25/15 in the FA, IN-FVPTC, NIFTP groups, respectively (Table 1). Given the VEGF immunohistochemical staining scores, mean scores did not differ significantly among the groups in terms of both intensity and percentage (Table 2). However, although there was no statistically significant difference, the total VEGF immunohistochemical staining score of the NIFTP group was higher than the scores of the FA (mean= 3.9 ± 1.8) and IN-FVPTC (mean= 4.3 ± 1.9) groups with a mean value of 4.6 ± 1.7, which was notable. When the FA, IN-FVPTC, and NIFTP groups were evaluated separately, there was no statistically significant difference between the tumor diameters (22.7 ± 13.9, 16.9 ± 9.6, 20.2

Table 1. Descriptive features of patients for folliculer adenoma (FA), invasive follicular variant thyroid papillary carcinoma (IN-FVPTC) and noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP)

	FA (n= 33)	IN-FVPTC (n= 41)	NIFTP (n= 40)	p
Female/Male	25/8	29/12	25/15	
Mean age ± SD*	44.7 ± 11.7	46.9 ± 13.6	43.2 ± 15.4	0.480
Mean tumor size ± SD	22.7 ± 13.9	16.9 ± 9.6	20.2 ± 12.4	0.125

*SD: Standard deviation.

Table 2. The expression characteristics of VEGF in all groups

	FA n %	IN-FVPTC n %	NIFTP n %	P
VEGF staining*				
0 (No staining)	4 12.1	3 7.3	2 5.0	
1 (Weak)	8 24.2	12 29.3	9 22.5	0.604
2 (Intermediate)	6 18.2	3 7.3	4 10.0	
3 (Strong)	15 45.5	23 56.1	25 62.5	
VEGF staining count (%)**				
<%30	10 30.3	12 29.2	8 20.0	
%30-60	13 39.4	9 22.0	12 30.0	0.313
>%60	10 30.3	20 48.8	20 50.0	
Scoring 1 (mean ± SD)	2.0 ± 0.8	2.2 ± 0.9	2.3 ± 0.8	0.269
Scoring 2 (mean ± SD)	1.9 ± 1.1	2.1 ± 1.1	2.3 ± 1.0	0.383
The sum of scores (mean ± SD)	3.9 ± 1.8	4.3 ± 1.9	4.6 ± 1.7	0.231

*Scoring 1: An intensity score.
**Scoring 2: A percentage of labeled thyrocytes score.

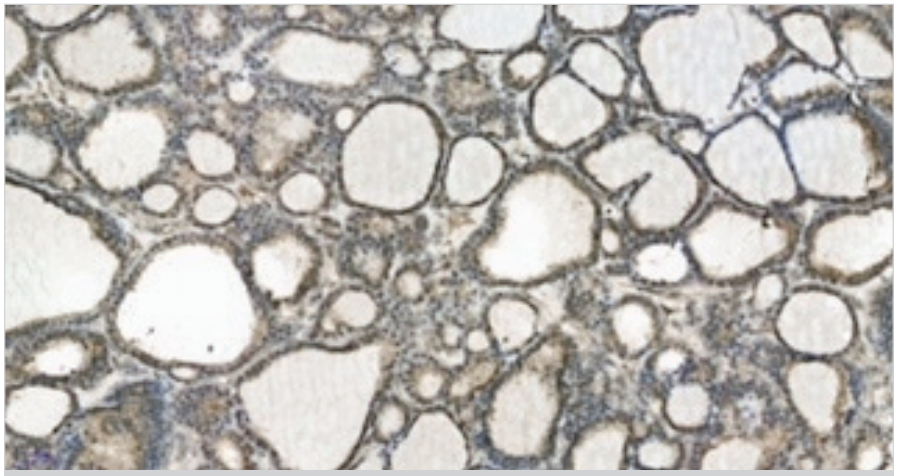

Figure 1. Strong expression of VEGF in cytoplasm of thyrocytes in NIFTP. Tumour cell staining 80%.

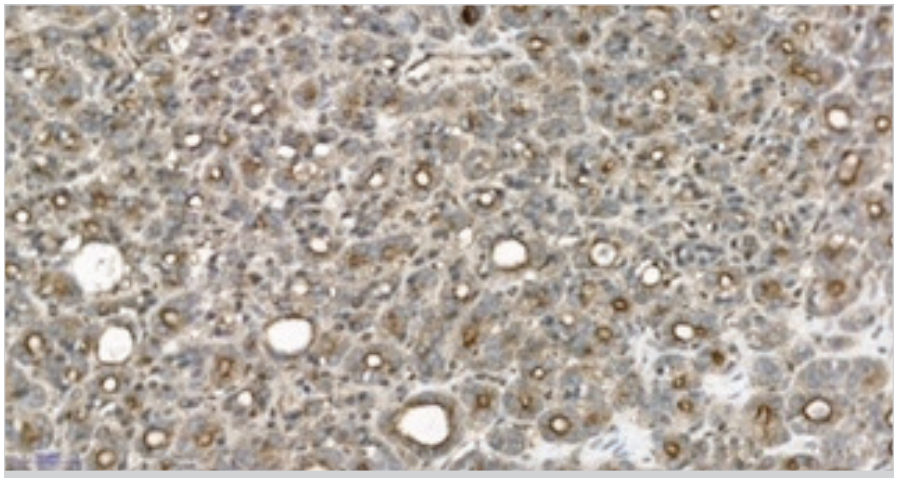

Figure 2. Strong expression of VEGF in cytoplasm of thyrocytes in FA. Tumour cell staining 80%.

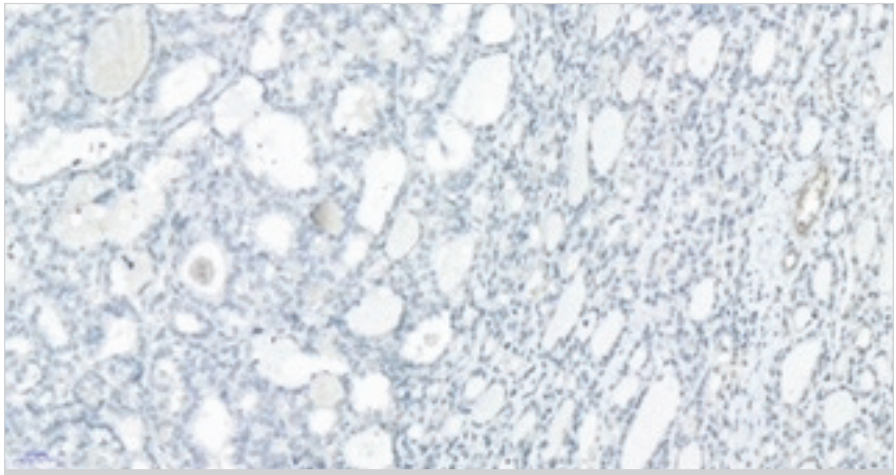

Figure 3. No expression of VEGF in NIFTP with positive internal control.

± 12.4, respectively) and the staining percentages. When evaluated based on tumor diameter regardless of the subgroup, mean percentage of VEGF immunohistochemical staining was 48.75 ± 29.46 in those with a tumor diameter of ≤10 mm and was 50.67 ± 29.92 in those with a tumor diameter of >10. Large tumors displayed more immunohistochemical staining, but this difference was not statistically significant. (p= 0.750).

DISCUSSION

Since the definition of NIFTP, the debates on its diagnosis, clinical behavior, treatment, and follow-up continue. As a matter of fact, the discussion of its papillary structure, BRAF V600E mutation and the presence of LNM in studies conducted after 2016 has led to a revision (7). Activating mutations of the RAS gene have been detected in 30-67% of NIFTP cases, which is one of the reasons that keep the debate on whether NIFTP may be a precursor lesion of invasive FVPTC alive. There is a hypothesis that NIFTP is actually a precursor lesion for cancer, and transformation occurs when it reaches a suitable size (19-22). It is known that a cytologically benign lesion has a very low probability of transforming into thyroid cancer in a long period of time. However, the debates on whether follicular adenoma and NIFTP may be precancerous lesions remain on the agenda. In our study, we participated in the discussions from a different perspective by demonstrating the immunostaining characteristics of VEGF-A, a potent stimulator of angiogenesis, in these three lesions. The question of whether NIFTP could be a precancerous lesion emerged with the results of two studies. One of these is the study of Parente. Parente et al. have retrospectively evaluated 102 patients previously diagnosed with PTC with a mean follow-up period of 5.7 years (range 0-11 years) (23). Of these patients, 2.1% were identified with NIFTP. They have reported LNM in 5% and distant metastasis (lung) in 1% of these patients who were identified with NIFTP. In another study, Cho et al. have evaluated their cohorts consisting of 152 encapsulated FVPTCs according to the revised criteria and found a central LNM rate of 3% when they interpreted it as NIFTP (24). There are studies showing a correlation between the expression level of VEGF and the aggressiveness of the tumor. It has been suggested that an idea can be obtained about tumor behavior in advance, considering this (25). In their studies, Klein et al. have shown that the VEGF immunostaining score was higher in those with LNM and systemic metastases (26). On the other hand, in their study conducted this year, Ria et al. emphasized that the serum level of VEGF, one of the angiogenic markers, was preoperatively higher in patients with PTC than those with benign goiter, and that its postoperative level decreased (27). In our study, more than 70% of the patients in the FA, IN-FVPTC and NIFTP groups showed a high percentage of VEGF immunostaining (>30%) (Table 2). This intense staining was more significant in the NIFTP group, although it was not statistically significant. This result may support the hypothesis that NIFTP may be a precancerous lesion for PTC whom has been emphasized to show high VEGF expression in studies. With another comment, it can be suggested that VEGF increases neovascularization in the early stage of PTC (lesion stage defined as NIFTP today). We are of the opinion that the result we obtained in our study would be statistically significant when studied with a larger number of patients, yielding an answer to this question. In another study on the place of NIFTP in the development process of PTC, Giannini et al. have analyzed mRNA expression and evaluated the difference of NIFTP from FA and infiltrative FVPTC (IFVPTC) (22). In this study, samples were divided into two groups on the basis of FA and IFVPTC expression types, NIFTPs were equally distributed in these groups with their mRNA expression characteristics. Since RNA expression types were similar to those of FA in some of the NIFTPs, while others were similar to those of IFVPTC. They also performed mutation analysis for their patients with NIFTP and found mutations with low oncogenic potential. Interestingly, they identified BRAFV600E mutation in one patient. They interpreted that NIFTP could indeed be a precancerous lesion for IFVPTC or classical PTC, except that this could be a technical error. If BRAFV600E is detected again in future studies, the precancerous lesion option will surely come to the fore. Thus, if NIFTP lesion exhibiting mRNA expression and genetic heterogeneity carries BRAF, RAS or other mutations, it may be a precursor of IFVPTC or PTC, while those without mutation will be FA-like benign lesions. We thought that VEGF-A immunohistochemical staining characteristics observed among the groups in our study might have a similar meaning to the results of this study. There was a significant VEGF-A expression in all three groups, but the distribution characteristic in the NIFTP group made us interpret that it could turn into a benign or malignant characteristic. Another result that drew our attention in our study was that the VEGF immunohistochemical staining scores of follicular adenoma, which is considered a benign lesion, were not much lower than those of the other two lesions. Contrary to other studies, this may suggest that VEGF, hence angiogenesis, is not always sufficient to evaluate the aggressiveness of the tumor, as well as brings to mind the question of whether follicular adenoma is a precancerous lesion, which has been discussed for years (28). The answers to these questions will be found with the increase in studies in this respect.

In conclusion, we observed that the total VEGF immunohistochemical staining score was higher in the NIFTP group than in the FA and IN-FVPTC groups in our study. There is no current literature about VEGF expression of NIFTP. Our study is the first study in the literature analyzing malignancy potential of NIFTP with VEGF analysis. Therefore, we think that with this point of view, we contributed to the debates that NIFTP is not a benign lesion but a precancerous lesion for PTC. Studies with an in-

creased number of patients will give a better idea. There are no definitive recommendations for follow-up and treatment due to the question marks about NIFTP. The American Thyroid Association does not require but recommends follow-up with serum thyroglobulin and cervical ultrasound, especially for high-risk patients (6). We think that there is a need for a large series of patients with long-term follow-up for the diagnosis of NIFTP to reassure surgeons and endocrinologists in terms of the patient's clinical course and treatment. It would be an appropriate approach to be careful in the follow-up and treatment of NIFTP, which is thought to be a borderline RAS lineage tumor between follicular adenoma and invasive FVPTC since its definition.

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Folikuler hücreden kaynaklanan tiroid neoplazilerinde 'Vascular Endothelial Growth Factor' ekspresyonu: NIFTP benign mi prekanseröz mü?

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ÖZET

Giriş ve Amaç: Vasküler endotelyal büyüme faktörü (VEGF) tiroidin fizyolojik ve patolojik anjiyogenezinde önemli rol oynar. Çalışmamızın amacı tiroidin folikuler hücre kaynaklı lezyonlarının VEGF ekspresyon özelliklerini belirleyerek papiller yapıda çekirdek özellikleri gösteren noninvaziv foliküler tiroit neoplazi (NIFTP) lezyonlarının prekanseröz olup olmadığını bu yolla değerlendirmek.

Gereç ve Yöntem: 33 folikuler adenom (FA), 41 invaziv folikuler varyant papiller tiroid kanseri ve 40 NIFTP tanısı olan hastanın tiroidektomi materyali retrospektif olarak değerlendirildi. 5-µm parafin kesitlerde VEGF immun boyama yapıldı. Belirlenen yüzdesel orana (boyanma yok; 0, %<30; 1, %31-60; 2, %>60; 3) ve boyanma yoğunluğuna göre (boyanma yok; 0, zayıf; 1 orta; 2, yoğun; 3) skorlama yapıldı. İki farklı skor kategorisinden total skor elde edildi.

Bulgular: FA, İN- FVPTK ve NIFTP gruplarında ortalama yaş sırasıyla 44,7 ± 11.7, 46,9 ± 13,6, 43,2 ± 15,4 yıldı. VEGF immun boyanma yüzdesi ise sırayla 44,7 ± 29,3, 50,2 ± 32, 54,4 ± 26,3 bulundu. İstatistiki olarak anlamlı olmasa da (p= 0,347) NIFTP grubunda total skor ortalama 4,6 ± 1,7 değeri ile FA (ort= 3,9 ± 1,8) ve İN-FVPTK (ort= 4,3 ± 1,9) daha yüksekti. Bu sonuç dikkat çekiciydi. Tümör çapları ile VEGF boyanma yüzdeleri arasında istatistiki anlamlılık yoktu.

Sonuç: İstatistiki anlamlılık olmasa da VEGF immun boyanma NIFTP lezyonlarda yüksek saptandı. VEGF'nin tümörogenezdeki rolü dikkate alındığında bu sonuç 'NIFTP lezyonlar papiller tiroid kanserinin öncüsü olabilir mi?' hipotezini desteklemektedir. Geniş kapsamlı çalışmalar yapılması NIFTP lezyonların patolojik yerini anlamada bu hipoteze katkı sağlayabilecektir.

Anahtar Kelimeler: VEGF, NIFTP, tiroidin folikuler lezyonları

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