Section: Pathology

Original Research Article

STUDY ON IMMUNOHISTOCHEMICAL ANALYSIS OF CD56 AND GALECTIN-3 EXPRESSION IN FOLLICULAR NEOPLASM OF THYROID

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Abstract

Background: Thyroid cancer, a common endocrine malignancy, is predominantly found in women and rarely in children, with follicular thyroid cancer being the second most common thyroid malignancy. This study aimed to investigate the immunohistochemical expression of CD56 and GALECTIN 3 in both benign and malignant thyroid follicular tumours, assess the significance of these markers in follicular neoplasms, and determine their diagnostic utility. **Materials and Methods:** This retrospective study included 45 cases of benign and malignant thyroid follicular tumours diagnosed using Hematoxylin and Eosin stain in the Department of Pathology, Tirunelveli Medical College between June 2014 and June 2017. Details regarding gross findings such as lesion size, capsular (thick or thin) details, and histopathological diagnosis were collected from the general surgical report register. **Result:** Females (82%) were more commonly affected by thyroid follicular adenoma and carcinoma than males (18%), with 93% exhibiting nodular lesions, and 59% of the cases had a nodule size > 4 cm.CD56 expression was found to be higher in follicular adenomas (96.6%), than in follicular thyroid carcinomas (16.6%), and Galectin-3 expression was 83.3% in follicular thyroid carcinomas, with only 3.03% in follicular adenomas. Loss of expression of CD56 is a more specific for follicular thyroid carcinoma, while Galectin-3 is reliable in distinguishing follicular adenomas from carcinomas. Combining CD56 and Galectin-3 increased the sensitivity and specificity, with Galectin-3 showing the highest sensitivity (83%).The combination of these markers improves the specificity for malignancy. **Conclusion:** A combination panel of CD56 and GALECTIN 3 is useful for increasing the chances of detecting thyroid malignancies.

INTRODUCTION

Thyroid cancer is the most common endocrine malignancy, among which 95% originate from thyroid follicular epithelial cells.[1] Worldwide, the incidence of thyroid cancer is approximately three to four times higher among women than men, and it is ranked as the sixth most common malignancy diagnosed in women. Most tumors are common between the third and sixth decade of life and rare in childhood.[2] Follicular adenoma and follicular carcinoma of the thyroid are tumours of epithelial origin with follicular cell differentiation. Of them, the incidence of follicular adenoma was 3% and 4.3%, as reported in two autopsy series.[3,4]

Follicular Thyroid Cancer (FTC) is the second most common thyroid gland malignancy after Papillary Thyroid Carcinoma (PTC). Follicular neoplasms of the thyroid are classified as benign or malignant depending on the presence or absence of capsular and vascular permeation. However, evaluating these features in histopathology is challenging, as incomplete capsular or equivocal vascular invasion due to processing or sectioning artefacts results in an inconclusive or inaccurate diagnosis.[5] Distinguishing Follicular thyroid carcinomas (FTC), especially Minimally Invasive Follicular Carcinoma (MIFC) of the thyroid, from the most common neoplasm of the thyroid, follicular thyroid adenoma, is very challenging, leading to avoidable surgery and exposing the patients to persuasive postoperative complications. Recent studies have focused on identifying immunohistochemical markers that may help in differentiating benign from malignant follicular thyroid tumours.[6] Estimating CD56 and GALECTIN 3 expression levels may help to differentiate between malignant and benign follicular thyroid neoplasms.

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Aim

This study aimed to investigate the immunohistochemical expression of CD56 and GALECTIN 3 in both benign and malignant thyroid follicular tumours, assessing the significance of these markers in follicular neoplasms, and to determine their diagnostic utility.

MATERIALS AND METHODS

This retrospective study was conducted from June 2014 to June 2017, involving 45 cases of benign and malignant follicular thyroid tumours that were diagnosed using Hematoxylin and Eosin stain in the Department of Pathology, Tirunelveli Medical College. Ethical committee approval was obtained before the study started.

This study included all cases reported as follicular adenoma and its variants, including follicular carcinoma of the thyroid and its variants, using Hematoxylin and Eosin (H&E) stain. Thyroid tumours other than follicular tumours, autolysed specimens, poorly processed material, and cases of dense tissue necrosis were excluded.

A total of 45 cases of surgically resected follicular thyroid tumours, including both benign and malignant follicular thyroid tumours, were included. Of the 45 cases, 33 were benign follicular tumours that included (n=32) follicular adenoma and (n=1) hyalinising trabecular adenoma, and 12 cases were malignant follicular thyroid tumours that included (widely invasive follicular carcinoma (n=4), minimally invasive follicular carcinoma (n=7), and Hurthle cell carcinoma (n=1)).

Patient details, such as age, sex, ultrasonogram findings, previous thyroid surgeries, and FNAC reports, were collected from the clinical case sheets and Medical Records. Gross findings regarding the lesion size, capsular (thick or thin) details, and histopathological diagnosis were collected from the general surgical report register from June 2014 to June 2017.

Sections prepared from 10% formalin-fixed paraffin-embedded blocks of benign and malignant follicular thyroid tumours were collected and stained using routine H&E staining. Immunohistochemical staining was done using CD56 and Galectin 3 markers for all the cases.

Membranous staining of follicular cells with CD56 was regarded as positive. The staining intensity of CD56 was graded on a scale of 0 to 3 where 0, 1+, 2+, and 3+ denotes no staining, weak/ slight staining, moderate staining and intense staining respectively, and the proportion of stained cells were interpreted as 0: <10% (For CD56, focal cytoplasmic and membranous reactivity of up to 10% was considered negative), 1+: 10-25%, 2+: >25-50%, 3+: >50 % .[7]

The cytoplasmic staining of follicular cells with Galectin 3 was regarded as positive .The intensity of Galectin-3 was graded on a scale of 0 to 3 where 0, 1+, 2+, and 3+ ,which denotes no staining, weak/ slight staining, moderate staining and intense staining respectively, and the proportion of stained cells were interpreted as 1+ (less than 5% of cells), 2+ (5% to 50% of cells) and 3+ (more than 50% of cells) .[8]

The study focused on CD56 and Galectin 3 immunohistochemical staining, highlighting the difficulty in distinguishing between membranous and cytoplasmic staining in some sections due to intense background staining. Background staining can be caused by non-specific antibodies binding to endogenous Fc receptors, hydrophobic-ionic interactions, and endogenous enzyme activity. To minimise background staining, an innocuous protein solution was added to the section before applying the primary antibody, allowing the primary antibody to bind to the antigenic site only. Blocking endogenous enzymatic activity before adding an enzyme-labelled secondary reagent prevents enzyme inactivation.

Statistical Analysis

Statistical analysis was performed using SSPS 11 software. Pearson Chi-square test with a 2x2 contingency table was used to calculate the p-value to ascertain statistical significance. Probability (p) values less than 0.05 were considered statistically significant.

RESULTS

Our study included 45 patients with follicular thyroid tumours. Of these, 33 cases were benign (n=32, follicular adenoma; n=1, hyalinising trabecular adenoma), constituting 73%, and the remaining 12 cases were malignant (follicular thyroid carcinoma), constituting 27%.

In this study CD56 showed positive membranous expression in (96.6%)32 out of 33 benign (n=31 , follicular adenoma and n=1, HTA) cases with sensitivity of 97% and specificity of 83% , with Positive Predictive Value (PPV) 94% and Negative Predictive Value(NPV) 91% in diagnosing benign tumors. CD56 expression is only 16.6% (n=2 out of 12) in Follicular Thyroid Carcinoma (FTC) cases. But CD56 distinguished Follicular Adenoma (FA) from Follicular Thyroid Carcinoma (FTC) with significant difference(p value is < 0.0001).

CD56 expression is absent in 83.3% (10 out of 12) of Follicular Thyroid Carcinoma cases with sensitivity of 83% and specificity of 97%, with Positive and Negative Predictive Values (PPV and NPV) are 91% and 94% respectively in diagnosing malignant tumors and its p value is less than 0.0001. In this study Galectin 3 showed positive cytoplasmic expression in 83.3 %(10 out of 12) FTC cases and in FA its expression is only 3.03% (1 out of 33) cases with sensitivity of 83% and specificity of 97%, with PPV and NPV are 91% and 94% respectively in diagnosing malignant tumors. So in our study Galectin 3 expression is higher in malignant (FTC) tumors than in benign (FA)tumors.

The results of our study showed that CD56 had lost its expression or expressed less in malignant tumors than benign tumors. In follicular thyroid carcinoma

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the specificity of CD56 (as a negative marker)was highly remarkable in distinguishing benign from malignant thyroid tumors(Follicular adenoma from Follicular Carcinoma)and clearly explained the expression of Galectin-3 made significant difference between follicular thyroid adenoma and follicular carcinoma minimally invasive type. In this study Galectin-3 was specifically expressed by malignant thyroid tumors, showing that this molecule could be used as an adequate marker for malignant thyroid follicular cells.

In diagnosing follicular thyroid carcinoma,the sensitive marker in our study was Galectin 3, and the specific marker was CD56. When we combined two markers, we did not reach 100% specificity for malignancy, on the other hand values were increased when compared to expression of single marker.

Table 1: Demographic data of the study.

	No of cases	**Percentage**
Follicular adenoma	32	
Hyalinising trabecular adenoma	1	
Widely invasive follicular carcinoma (WIFC)	4	
Minimally invasive follicular carcinoma	7	
Hurthle cell carcinoma (HCC)	1	
Females	37	82
Male	8	18
Nodular lesions	42	93
Diffuse lesions	3	7
Age	Benign	Malignant
20 to 40 years	60	41
41 to 60 years	36	41
61 to 80 years	4	8
Size of lesion	Follicular adenoma	Follicular carcinoma
1 to 2cm	30% (n=10)	NIL
2 to 4cm	60% (n=20)	41% (n=5)
>4cm	10% (n=3)	59% (n=7)
Invasion in histopathology	Numberof follicular thyroid carcinoma cases	Percentage
Vascular invasion only	2	17
Capsular invasion only	5	41
Both	5	42

Females (82%) were more affected than males (18%) for both follicular adenoma and follicular carcinoma of the thyroid. The age group commonly affected by benign follicular tumours (follicular adenoma) was 20–63 years, with a median age of 37±9.47 and the age group commonly affected by malignant tumours (follicular carcinoma) was 30–70 years, with a median age of 42±14.2 SD.

Nodular lesions were observed in 93% (n=42) of patients, and diffuse lesions were observed in only 7% (n=3). Palpable thyroid nodules occur in 4–7% of the population, and up to 60–70% have a nonpalpable nodule that can be identified by ultrasound imaging of the thyroid gland. Seven out of 12 cases (59%) of follicular carcinoma and three out of 33 cases (10%) of follicular adenoma had a nodule size of > 4 cm [Table 1].

Table 2: Immunohistochemical scoring of CD 56 and galectin-3 expression in follicular adenoma and carcinoma of the thyroid

	Immunohistochemical scoring in follicular adenoma(n=33)				**Immunohistochemical scoring in follicular thyroid carcinoma(n=12)**			
	0	1+	2+	3+	0	1+	2+	3+
CD56		2	15	15			2	
Galectin 3			1			3	5	2
	Immunohistochemical scoring of CD56				Immunohistochemical scoring of Galectin 3			
	0	1+	2+	3+	0	1+	2+	3+
Minimally invasive follicular carcinoma			1			3	3	1
Hurthle cell carcinoma			1					
Widely invasive follicular carcinoma							2	1

CD56 expression was higher in follicular adenomas (n=32, 96.6%) and CD56 expression in follicular thyroid carcinomas only (n=2, 16.6%). GALECTIN 3 expression was higher in follicular thyroid carcinoma (n=10, 83.3%) than in follicular adenoma (n=1, 3.03%). In follicular adenoma, out of 33 cases, 2 cases showed 1+,15 cases showed 2+, and 15 cases showed 3+ positivity for CD56. Only one patient showed 1+ positivity for galectin 3.

In follicular thyroid carcinoma, 3 of 12 cases (minimally invasive follicular carcinoma) showed 1+, 5 cases (3 minimally invasive follicular carcinoma, two widely invasive follicular carcinoma) showed 2+, and 2 cases (1 minimally invasive follicular carcinoma, one widely invasive follicular

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carcinoma) showed 3+ positivity for galectin 3. Only two cases (one minimally invasive follicular carcinoma and one Hurthle cell carcinoma) showed 2+ positivity for CD 56 [Table 2].

Table 3: Comparison of benign and malignant tumours with various factors of the study

	Benign Tumors		Malignant tumors	
	CD56	**Galectin 3**	**CD56**	**Galectin 3**
Sensitivity	97%	3%	17%	83%
Specificity	83%	17%	3%	97%
Positive predictive value	94%	9%	6%	91%
Negative predictive value	91%	6%	9%	94%
Positive likelihood ratio	5.7	0.036	0.175	27.6
Negative likelihood ratio	0.036	5.7	27.6	0.175
95% confidence interval	13.09 – 1955.68	0.005-0.076	0.005-0.076	13.09 – 1955.68
Odds ratio	160	0.006	0.006	160
P value	<0.0001		<0.0001	

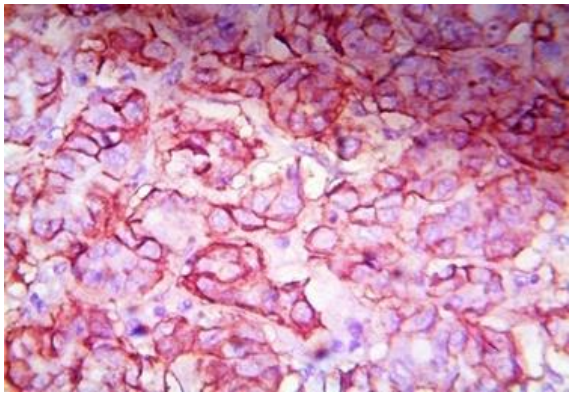

Figure 1: A case of follicular adenoma of thyroid showing CD 56 (3+)Membranous positivity(40x)

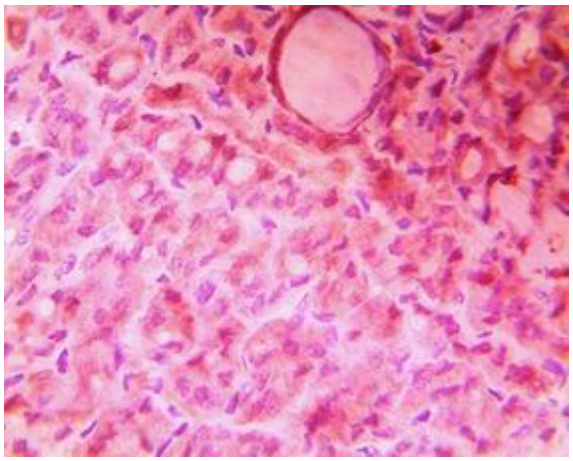

Figure 2: A case of follicular carcinoma with capsular invasion shows GALECTIN 3 (3+)-Cytoplasmic positivity(40x)

High rates (96.6%) of diffuse, strong, positive staining for CD56 were observed in follicular adenoma, whereas there were high rates (83.3%) of CD56 negativity in follicular thyroid carcinoma. Consistent with this finding, CD56 was found to be a more specific marker for follicular thyroid carcinoma. Galectin-3 is a reliable and sensitive marker for distinguishing follicular adenomas from follicular thyroid carcinomas.

A positive marker (Galectin-3) was added to the negative marker (CD56), and the sensitivity and specificity of the two markers, CD56 and galectin-3, were increased (83% and 97%, respectively). Hence, in differentiating benign from malignant follicular thyroid tumours, a panel of a combination of two markers (CD56 and Galectin-3) achieved a statistically significant difference, with a p-value of <0.0001. The highest sensitivity for thyroid follicular carcinoma was GALECTIN- 3 (83%), and the marker with the highest specificity was CD56 (97%) [Table 3].

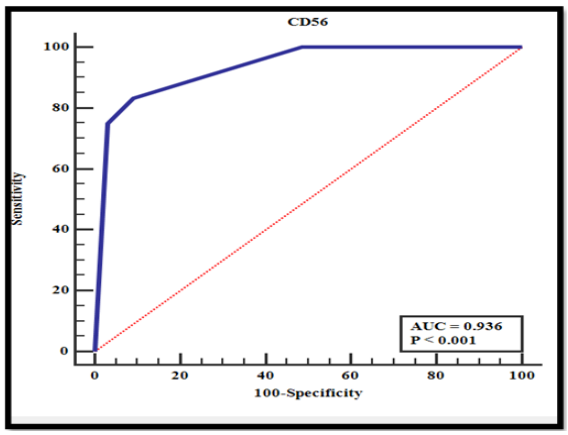

Figure 3: ROC curve of CD56

The area under the curve for CD56 as a negative marker was 0.936, with a 95% confidence interval (0.820–0.987), and the odds ratio was 160. Therefore, the AUC for CD56 (as a negative marker) was found to be a good parameter for detecting malignancies with a p-value < 0.0001 and showed a high sensitivity for follicular adenoma of the thyroid (97%). Galectin-3 showed a high sensitivity for thyroid follicular carcinoma (83%). As a negative marker, CD56 showed high specificity for follicular thyroid carcinoma (97%) [Figure 3].

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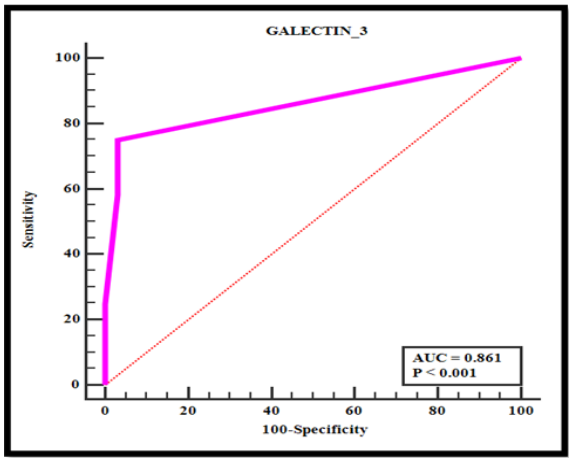

Figure 4: The ROC curve for the galectin 3.

The area under the curve for the galectin-3 marker was 0.861, with a 95% confidence interval (0.725–0.946) and an odds ratio of 160. Therefore, the AUC for galectin 3 was a good parameter for detecting malignancies, with a p-value of < 0.0001 [Figure 4]. When we combined CD56 and GALECTIN 3 markers, specificity increased for malignancy.

DISCUSSION

In this study, we analysed the expression of CD56 and GALECTIN 3 between follicular adenoma and follicular carcinoma of the thyroid. CD56 is a neural adhesion molecule (NCAM), an antigen related to follicular epithelial differentiation between follicular adenoma and follicular carcinoma of the thyroid. Many previous studies have revealed that CD56 expression is high in normal thyroid follicular cells and benign follicular lesions such as follicular adenomas and nodular hyperplasia. Reduced or loss of CD56 expression is correlated with tumour progression in patients. In papillary thyroid carcinoma, follicular thyroid carcinoma, and anaplastic thyroid carcinoma, CD56 expression is reduced or lost.

Scarpino et al. reported that 100% of follicular adenomas and 58.3% of Hurthle cell adenomas showed immunopositivity for CD56.[9] Park et al. found that 93.3% of follicular adenomas (FA) and 90.5% of Hurthle cell adenomas (HN) were positive for CD56.[10] El-Atti and Shash reported that 91.7% of Follicular adenoma (FA and 87.5% of cases of Hurthle cell adenoma (HN) and cases showed CD56 expression.[11] The studies of El-Demellawy et al. mentioned that expression of CD56 was found 100% in the studied cases of Hurthle cell adenoma (HN) and Follicular adenoma.[12]

Using CD56 as a negative marker, the sensitivity and specificity of CD56 were very impressive in distinguishing Follicular Thyroid Carcinoma from Follicular adenoma and in distinguishing papillary carcinoma-follicular variant (FVPC) from follicular adenoma of the thyroid (FA). Conversely, El-Demellawy et al. agreed with the results that the highest specificity was attained in differentiating Follicular Thyroid Carcinoma (FTC) from Follicular Tumors with Undetermined Malignant Potential (FT-UMP). In agreement with those studies, our study reported a high positive expression of CD56 in follicular adenoma cases compared to follicular thyroid carcinoma cases.

In this present study, CD56 showed positive membranous expression in (96.6%) of 32 out of 33 benign (n=31, follicular adenoma, and n=1, HTA) cases with a sensitivity of 97% and specificity of 83%, with positive predictive value (PPV) 94% and negative predictive value (NPV) 91% in diagnosing benign tumours. CD56 expression was observed in only 16.6% (n=2 out of 12) of follicular thyroid carcinoma (FTC) cases. However, CD56 significantly distinguished follicular adenoma (FA) from follicular thyroid carcinoma (FTC) ($p < 0.0001$). CD56 expression was absent in 83.3% (10 out of 12) of follicular thyroid carcinoma cases, with a sensitivity of 83% and specificity of 97%, and positive and negative predictive values (PPV and NPV) of 91% and 94%, respectively, in diagnosing malignant tumours, with a p-value <0.0001.

Our study showed that CD56 lost its expression or was expressed less in malignant tumours than in benign tumours. In follicular thyroid carcinoma, the specificity of CD56 (as a negative marker) was highly remarkable in distinguishing benign from malignant thyroid tumours (follicular adenoma from Follicular Carcinoma). Variation among studies concerning the sensitivity and specificity of CD56 was substantial.[10,11,13]

Galectin-3 is a [beta]-galactoside-binding lectin with a molecular weight of 31 KD that plays a significant role in a few biological processes. It regulates cell-cell and cell-matrix interactions, adhesion, migration, and repair of damaged cells. It also plays a role in inflammation and neoplastic transformation. This marker has been implicated in regulating normal cellular proliferation, apoptosis, malignant transformation, and the metastasis of cancer cells. Many researchers have found that galectin-3 is useful in discriminating benign from malignant thyroid lesions.[14,15]

Saleh et al. have noticed the results recording that galectin-3 showed 85% sensitivity for immunohistochemical separation between carcinomas and benign nodules (positive in 27.5% of benign vs. 85.1% of malignant nodules). However, its specificity was only 72.4%. They also observed that benign follicular lesions (neoplastic and non-neoplastic) showed lower expression than malignant tumours .[16] Kovacs et al. found that the cytoplasmic expression of Galectin-3 is a useful marker in the differential diagnosis of solitary encapsulated thyroid tumours, especially minimally invasive follicular carcinoma of the thyroid. Galectin-3 can aid in distinguishing minimally invasive follicular carcinomas from follicular adenomas. Some authors considered true Galectin -Galectin-3-positive follicular adenoma as an indication of potentially early or incipient carcinoma, in which the capsular

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and vascular invasion has not been observed yet histologically.[17]

The reason for the contradictory results was explained by Park et al., who reported discrepancies in the frequency of galectin-3 immunoreactivity in benign lesions. He stated that this controversy may be due to the different antibody detection systems and the positive and negative staining cutoff values.[18] Galectin -3 was also expressed in places where the follicular cells were in large numbers in a highly inflamed area and cells without cytological atypia or with Hurthle-cell transformation. The most likely explanation for the galectin-3 expression of non-neoplastic follicular cells in an inflamed area may be the cytokines secreted by inflammatory cells.[19] According to this explanation, distinguishing between follicular adenomas and carcinomas based only on Galectin-3 positivity may be dangerous. Therefore, combining galectin 3 with other markers increases the sensitivity and specificity of deciding whether the lesion is benign or malignant. The best combination of immunohistochemical markers for detecting malignancy was CK-19 with Galectin- 3, and CD56 with HBME1 respectively.[20] Following the previous studies, CD56 and Galectin-3 were the best combinations in distinguishing follicular carcinoma from follicular adenoma of the thyroid.

In the present study, Galectin 3 showed positive cytoplasmic expression in 83.3% (10) of 12 FTC cases. In FA, its expression was only 3.03% (1 out of 33) of cases with a sensitivity of 83% and specificity of 97%, with PPV and NPV of 91% and 94%, respectively, in diagnosing malignant tumours. CD56 expression was only 16.6% (n=2 out of 12) in FTC (n=1 MIFC, n=1 HCC). Galectin 3 significantly distinguished follicular adenoma from follicular carcinoma ($p<0.0001$). Hence, Galectin-3 expression is higher in malignant (FTC) tumours than benign (FA) ones. The results of this study clearly explained that the cytoplasmic expression of Galectin-3 was significantly different between follicular thyroid adenoma and follicular carcinoma minimally invasive type.

In this study, Galectin-3 was specifically expressed in malignant thyroid tumours, indicating that this molecule could be used as a marker for malignant thyroid follicular cells. In diagnosing follicular thyroid carcinoma, the sensitive marker in our study was galectin 3, and the specific marker was CD56. When we combined the two markers, we did not reach 100%specificity for malignancy; however, values were increased compared to the expression of a single marker.

CONCLUSION

GALECTIN 3 is a sensitive marker of follicular thyroid carcinoma (FTC) (83%). Loss of CD56 expression was found to be highly specific for follicular thyroid carcinoma (97%). A combination of CD56 and galectin-3 markers was found to be more specific for thyroid follicular carcinoma. Immunoexpressed ions of CD 56 and GALECTIN 3 are hence postulated to be important ancillary tests in diagnosing follicular thyroid neoplasms, although they do not replace the conventional histopathological examination. Therefore, we concluded that a combination panel of CD56 and GALECTIN 3 is useful for increasing the chances of detecting follicular thyroid carcinomas.

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