International Journal of Medical Science and Clinical Invention 7(12): 5154-5161, 2020
DOI:10.18535/ijmsci/v7i12.05 **ICV: 77.2**
e-ISSN:2348-991X, p-ISSN: 2454-9576

Research Article

No Correlation Between Galectin-3 Expression and Clinicopathological Features of Minimally Invasive Follicular Thyroid Carcinoma: Study in Single Institution

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Abstract

Background. Galectin-3 has been suggested to involve in invasion and aggressive behaviour of several cancer. The aim of this study is to evaluate the immunoreactivity of Galectin-3 in minimally invasive follicular thyroid carcinoma (FTC) in an attempt to investigate its association with clinicopathology of minimally invasive FTC.

Method. This study included 46 selected paraffin embedded tissue blocks from surgically resected minimally invasive follicular thyroid carcinoma, consists of 23 cases of minimally invasive FTC capsular invasion only and 23 cases of minimally invasive FTC encapsulated angioinvasive**.** Immunohistochemistry staining for Galectin-3 were performed on all cases. Galectin-3 protein expression was observed in the cytoplasm and the nucleus of examined tissues.

Result. Forty-three (93.5%) samples had strong or moderate staining and 3 (6.5%) tumours had negative or weak staining. Positive immunoreactivity of Galectin-3 was found in 18/23 (78.3%) cases of FTC capsular invasion only and 20/23 (86.9%) cases of FTC encapsulated angioinvasive. The galectin-3 did not show association with the sex (p=0.345), age (p=0.200), and tumour size (p=0.767). There was no significant difference of Galectin-3 immunohistochemical expression between minimally invasive FTC capsular invasion only and encapsulated angioinvasive (p= 0.699).

Conclusion. No differentiation of sex, age, tumour size, and immunohistochemical expression of galectin-3 in capsular invasion only and encapsulated angioinvasive of minimally invasive FTC.

Key words: galectin-3, immunohistochemistry, minimally invasive follicular carcinoma thyroid

Introduction

Follicular thyroid carcinoma (FTC) is a thyroid malignancy arising from follicular cells in which the diagnostic nuclear features of papillary thyroid carcinoma (PTC) are absent. The lesions are usually encapsulated and show invasive growth.[1] Follicular thyroid carcinoma (FTC) is the second most common malignancy originating from thyroid follicular cells. A pathological examination of surgical specimens is usually conducted to diagnose FTC based on the presence of capsular and/or vascular invasion, unless no distant metastases were detected at surgery. Based on the degree of invasion, FTC are divided into two categories: minimally invasive and widely invasive FTC.[2] Minimally invasive FTCs have a better prognosis than widely invasive FTC, but the prognosis of patients with certain characteristics such as old age, large tumour size and high-frequent vascular invasion is often poor.[3] Based on the invasion, minimally invasive FTC are divided into two categories: capsular invasion only and encapsulated angioinvasive. Invasion is a hallmark in FTC diagnosis.[2]

Galectin-3 a member of the galectin family is an endogenous β-galactoside binding lectin.

Galectin-3 (Gal-3), formerly known as CBP35, Mac-2, εBP, is predominantly localized in the cytoplasm. It can translocate to the nucleus from the cytoplasm via nonclassical secretion pathway after it is synthesized on the cytoplasmic ribosomes. This protein is expressed by human neutrophils, macrophages and mast cells, and Langerhans cells, through which it could also be involved in inflammatory processes. It has been found to be associated with cell adhesion, recognition, proliferation, differentiation, immunomodulation, angiogenesis, apoptosis and can be a reliable marker for cancer aggressiveness (invasion ability and metastasis). Galectin-3 plays an important role in invasion of various types of cancer, including hepatocellular carcinoma, meningioma, ovarian carcinoma, oral squamous cell carcinoma, and thyroid cancer. Previous studies reported that Galectin-3 is a specific immunohistochemical marker in diagnosing FTC. The expression of galectin-3 is associated with tumour progression and metastatic potential in thyroid cancers.[4-7] This study aims to verify protein expression of Galectin-3 in minimally invasive FTC and correlate the results with the clinicopathological aspects.

Material and Methods

This research has ethical clearance from Health Research Ethics Committee, Hasan Sadikin Hospital, number LB.02.01/X.6.5/152/2020, with a waiver of informed consent.

Patients

All study materials were paraffin blocks of patients who had surgery and had been diagnosed histopathologically as minimally invasive follicular thyroid carcinoma at Hasan Sadikin General Hospital, Bandung, Indonesia between January 1st 2011 – 31st December 2018. Fourty-six cases of minimally invasive follicular thyroid carcinoma, consists of 23 cases of FTC capsular invasion only and 23 cases of FTC encapsulated angioinvasive were included in this study.

Histology process and immunohistological (IHC) stains.

All specimens were fixed in 10% buffered neutral formalin and embedded in paraffin. All slides from each case were reviewed by two experiences pathologists. IHC techniques were performed on selected sections to detect expression levels Galectin-3. Specimens in paraffin blocks were cut to 4-μm sections. Immunohistochemistry was performed using labelled streptavidin biotin immunoperoxidase complex method with Starr trek universal HRP detection system (Biocare medical). Primary antibodies included was mouse monoclonal antibody to Galectin-3 (Catalogue Number: BZ-084560F-AM, Bioenzy, Shanghai China, at 1: 400 dilution). The procedure used for immunohistochemistry was as follows: 4μ thick sections were cut on 0.01% poly-L-lysine coated glass slides and baked at 60°C for one hour on a standard histology hotplate. Sections were dewaxed in xylene and treated with three changes of ethanol and alcohol then brought to water. Sections were subjected to heat induced antigen retrieval in a decloaking chamber (DC2008INTL, Biocare medical., USA) in EDTA (pH 8.0). Cooling at room temperature for 20 minutes followed this. Sections were then treated to block endogenous peroxidase, stained with primary antibodies and incubated for 1 hour at room temperature. Detection was done by horseradish peroxidase polymer-based detection system (Biocare medical), diaminobenzidine chromogen and counterstain with haematoxylin. Positive immunohistochemical control slides were colorectal adenocarcinoma for Galectin-3. Negative immunohistochemical control sections are made by exclusion of the primary antibody.

IHC analysis and interpretation

Authors independently evaluated the slides and determined the mean percentage (%) of positive (PP) cells and the staining intensity (SI) at different high-power fields (400x) using Olympus CX21 light microscope. Immunoreactivity for Galectin-3 was identified by the presence of cytoplasm and /or nucleus brown staining of tumour cells. The intensity of Galectin-3 were graded semi quantitatively on a scale 0-3 (0, no staining; 1+, weak staining; 2+, moderate staining; 3+, strong staining) and distribution of stained tumour cell was graded semi quantitatively on a scale 0-4 (0, negative; 1+, <25%; 2+, 25-50%; 3+, 50-75%; 4+, >75%). Then, the average weighted score (AWS) for each area was calculated by multiplying PP by the SI (score 0-12). The results were score as negative (0-6) and positive (≥7).

Statistical analysis

The comparison between Galectin-3 immunoreactivity in minimally invasive FTC capsular invasion only and encapsulated angioinvasive was evaluated using chi-square test. $p<0.05$ is considered statistically significant. Statistical tests were performed using the software SPSS 24.0 version.

Results

Clinicopathological characteristics of patients

This study included 46 patients, age range between 12-73 years old, their mean age was 47 years old. Thirty-one patients were female and 15 were male. Tumour size ≤ 4 consisted of 25 cases and > 4 in 21 cases. Patient characteristics are presented in table 1

Comparison of clinicopathology between minimally invasive FTC capsular invasion only and encapsulated angioinvasive

The proportions between age, sex and tumour size in the minimally invasive FTC capsular invasion only and encapsulated angioinvasive groups were compared. For the analysis of the categorical data, namely age, sex and tumour size in the table were tested using the Chi-Square statistical test. The results of statistical tests in the research group above obtained information on the *p*-value of the variable age, gender and tumour size greater than 0.05 (*p*-value> 0.05) which means that it is not statistically significant or thus it can state that there is no difference between age, sex and tumour size in the minimally invasive FTC capsular invasion only and encapsulated angioinvasive groups. Comparison between minimally invasive FTC capsular invasion only and encapsulated angioinvasive groups are presented in table 2.

Table 1. Clinicopathological characteristics of the patients

Variable	N=46
Age (years)	
Mean±Std	47.07±14.344
Median	48.00
Range (min-max)	12.00-73.00
<55 tahun	32(69.6%)
>55 tahun	14(30.4%)
Sex	
Male	15(32.6%)
Female	31(67.4%)
Histopathology	
Folicullar Carcinoma	
Minimally invasive	
Capsular invasion only	23 (50%)
Encapsulated angioinvasive	23(50%)
Tumour size	
≤ 4	25(54.3%)
> 4	21(45.7%)

Table 2. Clinicopathological characteristics of the patients between minimally invasive FTC capsular invasion and encapsulated angioinvasive

Variable	Minimally invasive FTC capsular invasion only N=23	Minimally invasive FTC encapsulated angioinvasive N=23	*p*-value
Age (years)			0.200
<55	18 (78.3%)	14 (60.9%)	
>55	5 (21.7%)	9 (39.1%)	
Sex			0.345
Male	6 (26.1%)	9 (39.1%)	
Female	17 (73.9%)	14 (60.9%)	
Tumour size			0.767
≤ 4	13 (56.5%)	11 (47.8%)	
> 4	10 (43.5%)	12 (52.2%)	

Immunohistochemical intensity, distribution and histoscore of Galectin-3

The immunoreactivity of Galectin-3 in minimally invasive FTC was detected in the cell cytoplasm and also stained nuclear cell as illustrated in figure 1. The immunohistochemical histoscore, intensity and distribution of Galectin-3 were shown in table 3. Most of FTCs showed moderate to strong Galectin-3 intensity. Analyzing the distribution of tumours in our study, for the positivity of galectin-3, we found that Galectin-3 tend to distribute in >80% tumour cells. There were no significant difference of Galectin-3 immunohistochemical histoscore between minimally invasive FTC capsular invasion only and encapsulated angioinvasive (p= 0.699). There was no significant difference between Galectin-3 immunohistochemical intensity and distribution between minimally invasive FTC Capsular invasion only and FTC encapsulated angioinvasive. Galectin-3 tend to show diffuse staining in minimally invasive FTC capsular invasion only and encapsulated angioinvasive.

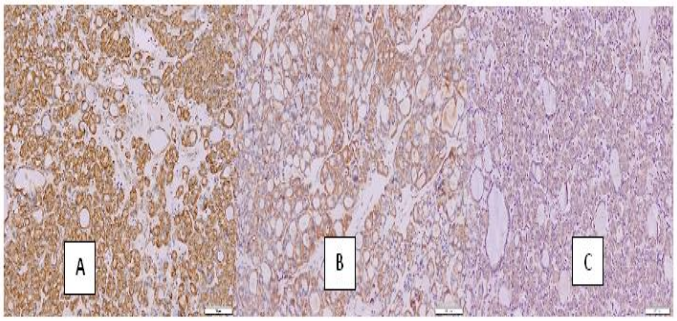

Figure 1. Galectin-3 Immunoexpression in minimally invasive FTC, A. Strong intensity of staining (+3), B. Moderate intensity of staining (+2), C. Weak intensity of staining (+1)

For analysis on categorical data, namely Galectin-3 Intensity and Galectin-3 Distribution in the table 3, it was tested using the Kolmogorov Smirnov statistical test while the Galectin-3 histoscore variable was tested using the Fisher Exact Test. The results of statistical tests in the research group above obtained information on the *p*-value of the Galectin-3 intensity, Galectin-3 distribution and Galectin-3 histoscore greater than 0.05 (*p*-value > 0.05) which means that it is not statistically significant, thus it can be explained that there was no statistically significant difference in percentage between the variables of Galectin-3 intensity, Galectin-3 distribution and Galectin-3 histoscore in the minimally invasive FTC capsular invasion only and encapsulated angioinvasive groups. Most of FTC tumour cells showed diffuse >80% and strong Galectin-3 staining.

Immunohistochemical distribution and intensity of Galectin-3 at the invasive front of minimally invasive FTC

Immunohistochemical distribution and intensity of Galectin-3 at the invasive front of minimally invasive FTC were shown in table 4. Compared to overall area of minimally invasive FTC tumour, the intensity and distribution of Galectin-3 immunostaining at the minimally invasive FTC invasive front were stronger.

Table 3. Immunohistochemical intensity, distribution and histoscore of Galectin-3

Immunohistochemistry	**Minimally invasive FTC capsular invasion only N=23**	**Minimally invasive FTC encapsulated angioinvasive N=23**	***p*-value**
Galectin-3 intensity			**1.000**
Negative	0(0.0%)	0(0.0%)	
Weak	1(4.3%)	2(8.7%)	
Moderate	6(26.1%)	7(30.4%)	
Strong	16(69.6%)	14(60.9%)	
Galectin-3 distribution			**0.414**
Negative	0(0.0%)	0(0.0%)	
<20%	4(17.4%)	1(4.3%)	
20-50%	2(8.7%)	1(4.3%)	
50-80%	7(30.4%)	5(21.7%)	
>80%	10(43.5%)	16(69.6%)	

Galectin-3 histoscore			**0.699**
Mean±Std	8.35±3.563	9.22±3.162	
Median	9.00	9.00	
Range (min-max)	1.00-12.00	1.00-12.00	
≥ 7	18(78.3%)	20(87.0)	
<7	5(21.7%)	3(13.0%)	

Table 4. Immunohistochemical intensity, distribution and histoscore of Rac1 and Galectin-3 at the invasive front of minimally invasive FTC

Immunohistochemistry	**FTC N=46**
Galectin-3 Intensity	
Negative	0(0.0%)
Weak	0(0.0%)
Moderate	11(23.9%)
Strong	35(76.1%)
Galectin-3 Distribution	
Negative	0(0.0%)
<20%	0(0.0%)
20-50%	0(0.0%)
50-80%	1(2.2%)
>80%	45(97.8%)

Comparison of clinicopathology between minimally invasive FTC high histoscore and low histoscore

For the analysis of categorical data, age and gender in were tested using the Chi-Square statistical test, while the histopathology and tumour size were tested using the Fisher Exact Test. The results of statistical tests in the research group obtained information on the *p*-value of the variables age, gender, histopathology and tumour size greater than 0.05 (*p*-value> 0.05) which means that it is not statistically significant, thus it can be explained that there is no difference in the percentage between the variables age, gender, histopathology and tumour size in the low and high histoscore groups.

Table 5. Clinicopathological characteristics of the patients between high histoscore and low histoscore of Galectin-3 immunohistochemistry

Variable	**Low histoscore N= 8 (17.4%)**	**High histoscore N = 38 (82,6%)**	***p*-value**
Age (years)			0.225
<55	7 (87.5%)	26 (68.4%)	
>55	1 (12.5%)	12 (31.6%)	
Sex			0.613
Male	2 (25%)	12 (34.2%)	
Female	6 (75%)	25(65.8%)	
Histopathology			0.699
Folicullar Carcinoma			
Minimally invasive			
Capsular invasion only	5 (62.5%)	18 (47.4%)	
Encapsulated angioinvasive	3 (37.5%)	20 (52.6%)	
Tumour size			1.000
≤ 4	4 (50%)	17 (44.7%)	
> 4	4 (50%)	21 (55.3%)	

Discussion

In this present study the mean age of the study subjects was 47 years with an age range from 12-73 years. This is consistent with the literature that states that thyroid nodule lesions are frequent in adulthood with the incidence rate increasing with age, the average peak in the fifth and sixth decades. In line with this study, Susilo et al study

stated that the highest number of thyroid nodule lesions was at the age of 31-40 years old.[8] Another study by Roosandris et al, follicular thyroid carcinoma was highest in the age range 44-51 years.[9]

In this study, it was found that most of patients were female. The number of female sufferers is more than that of men, namely as much as 31 (67,4%). Ratio between male and female 1: 2. This is in accordance with the literature which states that the incidence of follicular thyroid nodules is higher in women than men.[1] This is in accordance with previous research by Meixner et al which stated that the incidence of FTC was 2-4 times more than that of men so that the possibility of the involvement of certain genes that react with sex hormone receptors in the development of FTC needs to be further investigated.[10] The size of the tumour used in this study used 4 cm cut off. In the study, Ito et al stated that tumour size > 4 cm had a significant effect on the prognosis of widely invasive FTC. In this study it was found that tumour size ≤ 4 cm was 25 (54,3%) and > 4 cm was 21 (45.7%).[11] We investigated the potential clinical relevance of the variable age, gender and tumour size in the minimally invasive FTC capsular invasion only and encapsulated angioinvasive groups. All of the variable showed no statistically significant (*p*-value > 0.05).

In the present study we also investigated the potential clinical relevance of galectin-3 expression in minimally invasive FTC. Several attempts are reported exploring galectin-3 expression as a diagnostic indicator in FTC. The mechanisms underlying the role of galectin-3 in carcinogenesis are not clearly defined, but these probably involve the regulation of intracellular signal pathways. Galectin-3 gene contains a responsive element to the tumour suppressor p53 and it is downregulated by p53. Also, Galectin-3 was reported to exhibit an anti-apoptotic activity, due to its considerable similarity to Bcl2, thereby promoting survival of malignant cells.[12] Galectin-3 has received significant attention as a diagnostic marker for thyroid cancer, showing different expression of thyroid carcinoma compared with benign and normal thyroid specimens.[13]

Many previous studies have found that galectin 3 plays an important role in various types of cancer. A positive correlation between the expression of galectin-3 and tumour progression has been observed in colorectal, mammae, thyroid, and lung cancer. In addition to its expression levels, galectin-3 localization pattern seems to play a role in cancer progressions.[12]

Many researchers had evaluated the staining pattern of galectin-3 in other malignant tissues. Some have detected galectin-3 in the cytoplasm and nucleus of normal cells and predominantly in the cytoplasm of cancer cells in thyroid, colon, prostate and tongue cancer. Study by Oestreicher et al., stated that Galectin-3 was expressed in minimally invasive FTC.[14] Many studies reviewed by Chiu et al., showed positive expression of Galectin-3 ranged from 33%-100% cases of FTC.[15] The largest series, reported by Bartolazzi et al, identified Galectin-3 expression in 95% (54/57) of FTC cases.[16]

In this study, it was found that almost all samples of minimally invasive FTC expressed galectin-3, this supports several previous studies which stated that almost all samples of thyroid malignant lesions express galectin-3. In this study, galectin-3 was found in the cytoplasm and some of them in the nucleus of tumour cells. Yoshii *et al*, detected galectin-3 immunoreactivity in cytoplasm of thyroid papillary carcinoma cells and it could also be detected in cell nucleus, cell surface or outside cell.[17]

Few studies investigated Galectin-3 expression in follicular thyroid carcinoma (FTC), positivity was encountered in minimally invasive FTC,[18] as well as in fully invasive FTC in a study of 260 cases which also correlated the galectin-3 positivity to the degree of capsular or vascular invasion. The concluded that Galectin-3 expression level significantly increased with the degree of vascular or capsular invasion ($p<0.0001$).[19, 20]

Only a few researchers have discussed the relationship between the immunohistochemical expression of galectin-3 and clinicopathology in cancers. Study by Aboulhagag et al in 67 samples of renal cell carcinoma were stained with galectin-3 showed no statistical significance of age ($p=0.226$), sex ($p=0.145$), and tumour size ($p=0.559$).[21] In the present study, we found no differentiation between the immunohistochemical

expression of galectin-3 and clinicopathological consist of sex, age, histopathological type and tumour size in the present study. Possibly, there was no statistical significance due to small number of tumours. We also observed there was no significant difference of Galectin-3 immunohistochemical expression between minimally invasive FTC capsular invasion only and encapsulated angioinvasive (p= 0.699).

Conclusion and Recommendation

In conclusion, our results suggest that no differentiation of immunohistochemical expression of galectin-3 in capsular invasion only and encapsulated angioinvasive of minimally invasive FTC. Further studies need to be done on a large sample of tumour tissues in all histopathology type of FTC.

Author Contributions

Conceptionalization: HA, Data curation: HA, RA. Formal analysis: HA, BSH Funding Acquisition: HA, BSH. Investigation: HA, SS, BSH. Methodology: HA, SS, BSH. Supervision: SS, BSH, Writing—original draft: HA, RA. Writing—review &editing: HA,RA, BSH. Approval of final manuscript: all authors.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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