Galectin-3 Immunohistochemical Expression in Thyroid Neoplasms – A Study from Kalaburagi, Karnataka

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ABSTRACT

BACKGROUND

Thyroid carcinoma is the most common endocrine malignancy. Galectin-3 has been implicated in malignant transformation and metastasis of cancer cells and it has received notable recognition for its usefulness as a diagnostic marker for thyroid cancer. We wanted to evaluate the expression of Galectin-3 on thyroid neoplasms, establish its diagnostic accuracy and also differentiate between benign and malignant thyroid lesions.

METHODS

A total of 54 thyroidectomy specimens were studied over a period of 3 years (2016 - 2019) which included 20 benign and 34 malignant thyroid neoplasms. Histopathologic evaluation of H & E stained sections was done and immunohistochemistry (IHC) staining for Galectin-3 was performed for all neoplasms with the polymeric method using lyophilized mouse monoclonal antibody. (Path n Situ) and grading based on intensity of Galectin-3 expression were noted.

RESULTS

Galectin-3 expression was significantly higher ($P < 0.001$) in malignant thyroid neoplasms in comparison to the benign neoplasms. Galectin-3 expression for malignant neoplasms showed sensitivity of 88.23 %, specificity of 95.0 %, positive predictive value (PPV) of 96.8 % and negative predictive value (NPV) of 82.6 %. Galectin-3 expression in Papillary thyroid carcinoma showed a sensitivity of 95.83 % and PPV of 88.2 %. While comparing the neoplasms showing follicular pattern, Galectin-3 expression was more in the malignant neoplasms (follicular carcinoma and follicular variant of papillary carcinoma thyroid) than benign neoplasms (follicular adenoma).

CONCLUSIONS

Galectin-3 is a useful marker in differentiating benign and malignant thyroid neoplasms. Galectin-3 is sensitive for Papillary thyroid carcinoma (PTC) and among the follicular patterned lesions, Galectin-3 is sensitive for follicular variant of papillary carcinoma and follicular carcinoma. Thus Galectin-3 protein expression evaluated using immunohistochemistry technique acts as an adjunctive ancillary technique in thyroid cancer diagnosis.

KEYWORDS

Galectin-3, Immunohistochemistry, Thyroid Carcinoma, Papillary Thyroid Carcinoma

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BACKGROUND

Thyroid carcinoma is the most common endocrine malignancy and more than 95 % of thyroid carcinoma originates from follicular epithelial cells. The incidence of thyroid cancers is rapidly increasing in India particularly among the younger population (age group < 45). Most follicular cell derived carcinomas are well differentiated malignancies which can be treated effectively by surgical resection. Preoperative evaluation and establishing a diagnosis of apparently single thyroid nodule by fine needle aspiration cytology is challenging. In many cases especially in follicular - patterned thyroid lesions, even with histological analysis the diagnosis of neoplasm and distinction between benign and malignant neoplasm can be difficult. The decision favouring benign or malignant lesion has clinical consequence and implies different modalities of treatment. For this reason, the approach to these challenging tumours should include ancillary techniques like immunohistochemistry that can improve the standard morphologic assessment. Galectin-3 is a protein that binds to β – galactosidase residues on cell surface glycoproteins and has been identified in the cytoplasmic and nuclear compartment. Galectin-3 has been implicated in regulation of normal cellular proliferation and apoptosis, as well as malignant transformation and metastasis of cancer cells. In the recent times Galectin-3 has received notable recognition for its usefulness as a diagnostic marker for thyroid cancer; the utility assessed by studies have reported encouraging results. We wanted to evaluate the expression of Galectin-3 on thyroid neoplasms, establish its diagnostic accuracy and also differentiate between benign and malignant thyroid lesions.

METHODS

In this observational study done in Kalaburagi (IEC. Reg. No.: ECR / 889 / Inst. / KA / 2017) where we examined specimens from 54 consecutive patients who were operated for either benign or malignant thyroid disease and admitted at our institute from 2016 to 2019. Preoperative routine investigations like complete blood profile, bleeding and clotting time, USG findings and thyroid profile of the cases were noted. All lobectomy, isthmusectomy, hemithyroidectomy, subtotal, near total and total thyroidectomy specimens with macroscopically and microscopically detected neoplastic lesions were included. Cases where there were extensive tumour necrosis without sufficient viable tumour cells for accurate evaluation of results were excluded. The specimens were received in containers containing 10 % formalin and after overnight fixation, representative areas were selected for paraffin embedding. In case of encapsulated lesions, adequate representation from tumour capsule – thyroid interface was given. Sections were cut at 3 - 4 microns thick and stained with haematoxylin and eosin.

The histopathological evaluation was performed by two pathologists and the final diagnosis of the tumour histotype and subhistotype was made in accordance with World Health Organization classification. All cases had unambiguous histomorphology and there was 100 % agreement between the two pathologists. For statistical purposes the histopathologic diagnosis was considered the gold standard. Immunohistochemistry was carried on sections diagnosed as neoplastic lesions.

Immunohistochemical Determination of Galectin-3 Expression

The sections from the tumour were subjected to immunohistochemical staining using Lyophilized Mouse monoclonal antibody Galectin-3 in 1:100 dilutions. (Path n Situ). IHC was done by Polymer-based labelling, basic two – step method.

Staining Procedure

Neutral buffered formalin fixed paraffin embedded tissue sections of 2 to 3 µm were taken on poly L lysine coated slides. Slides were incubated at 60^0 C for one hour in oven. Deparaffinization and rehydration were done by two changes in xylene, three changes in graded alcohols followed by immersion in distilled water for 5 minutes. Antigen retrieval was done with Tris - EDTA (pH 8.5 to 6.2) using multi epitope retrieval system (MERS). Slides were brought to room temperature and washed with distilled water. Slides were then treated with endogenous peroxidase block for 10 minutes. Further, slides were washed in tris-buffered saline (TBS) wash buffer, 3 times for 3 minutes. Treated with power block for 10 minutes, the solution was allowed to drain. Primary antibody was applied for an hour. Washed with TBS wash buffer, 3 times for 3 minutes. Super enhancer was added, for 20 minutes. Secondary antibody i.e. Polymer HRP was applied for 30 minutes. Washed with TBS wash buffer, 3 times for 3 minutes. Diaminobenzidine (DAB) chromogen was applied for 5 minutes at room temperature. Washed with distilled water to stop chromogen reaction. Counter staining was done with Mayer's Haematoxylin for 2 minutes and then washed with tap water. Slides were then subjected to clearing and mounting.

IHC Staining Pattern

Galectin-3 produces both cytoplasmic and nuclear staining. Staining pattern was compared with control slides.

Immunohistochemical Scoring

The staining scores were assigned according to Katie B. Weber et al.[1] and Marille. E. Hermann et al.[2] Sections showing immunostaining in < 5 % of tumour cells were considered negative and sections showing immunostaining in > 5 % of tumour cells were further scored as follows

Score Staining Intensity

0 No staining
1 + Slight staining
2 + Moderate staining
3 + Intense staining.

Statistical Analysis

Statistical analysis was done using 2 x 2 contingency table. chi-square test with Yates correction was used to calculate P - value to ascertain statistical significance.

RESULTS

A total of 90 thyroidectomy specimens were received over a period of 3 years of which 54 cases (60 %) were neoplastic and 36 cases (40 %) were non-neoplastic. The 54 thyroid neoplasms were studied and analysed. Most of the cases encountered in the present study were from 3rd to 5th decade of life (50 %). The Mean and SD of age was 42.16 + / - 13.54. In the present study females constituted 81.48 % of the cases (N = 44) with a male to female ratio of 1: 4.4. Benign neoplasms accounted for 37.04 % of the lesions (20 cases) and malignant neoplasms accounted for 62.96 % of the lesions (34 cases). Majority of the patients presented with a solitary thyroid nodule – right (43 %) and majority had undergone hemithyroidectomy (41 %).

The benign lesions encountered were of 3 types of which the most common one was follicular adenoma accounting for 85.00 % (17 cases) of all benign neoplasms, of which normofollicular variant accounted for 58.8 % (N = 10), microfollicular variant accounted for 29.4 % (N = 5) and macrofollicular variant accounted for 11.76 % (N = 2). Two cases of Hurthle cell adenoma were encountered accounting for 10.00 % of benign lesions. A single case of Hyalinizing trabecular adenoma was also encountered.

The most common malignant neoplasm was papillary carcinoma accounting for 71 % (24 cases). Second most common malignant neoplasm was follicular carcinoma accounting for 18 % (6 cases). There were 2 cases of anaplastic carcinoma accounting for 6 %. Other less common lesions were one case of medullary carcinoma which was seen in a 40-year-old male. A single case of non-Hodgkin's lymphoma of diffuse thyroid with mixed small and large cell type was seen in a 48 year old female. Of the 24 cases of papillary carcinoma seen, classic variant was encountered in 18 cases, follicular variant was seen in 2 cases, encapsulated variant in 2 cases, tall cell variant in 1 case and micropapillary carcinoma was seen in 1 case.

Immunohistochemical Staining Results

Intensity of Galectin-3 staining varied from moderate / strong to weak or focal. Its localization was dominantly cytoplasmic but also membranous or nuclear in some cells. Amongst the benign lesions 95 % of them (19 cases) showed negative staining for Galectin-3 and 5 % (1 case) of them showed positive staining. Out of 17 cases of follicular adenoma, 15 cases (88.23 %) showed no staining, 1 case (5.88 %) showed focal / weak staining and one case showed moderate staining (5.88 %). Both the cases of Hurthle cell adenoma and a single case of Hyalinizing trabecular adenoma showed negative staining for Galectin-3. Amongst the malignant lesions 88.84 % (30 cases) showed positive staining and 11.76 % (4 cases) showed negative staining. Of the 24 cases of PTC, 21 cases (95.83 %) showed intense and diffuse staining (shown in Figure 1 a), 2 cases (8.33 %) showed moderate staining (2 +) 1 case (4.16 %) showed no staining. 2 cases of follicular variant of Papillary carcinoma showed positive staining (2 + / 3 +). (Shown in Figure 1b).

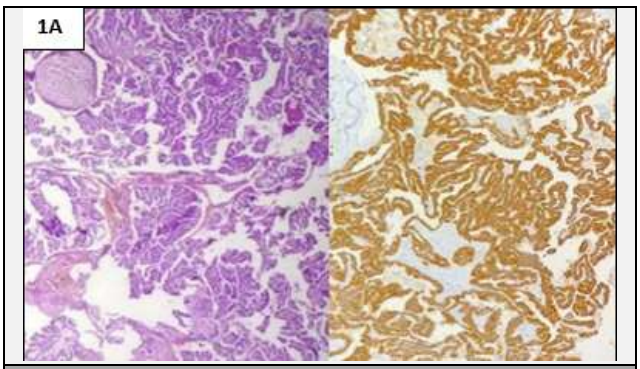

Figure 1A. H & E: 100X - Tumour Cells Showing Papillary Pattern of Arrangement and Papillae are Complex, Branching and Have Central Fibrovascular Core. IHC Galectin-3 ; 100X and Tumour Cells Show Intense and Diffuse Staining (3 +)

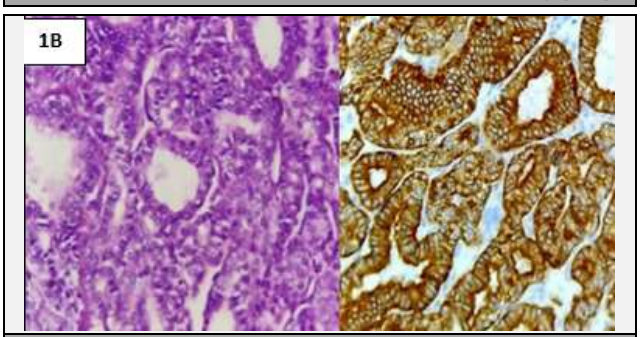

Figure 1B. H & E: 400X : Follicular Patterned Arrangement with Cells Showing Nuclear Clearing. IHC Galectin – 3 : 400X : Tumour Cells Showing Intense and Diffuse Cytoplasmic Staining (3 +)

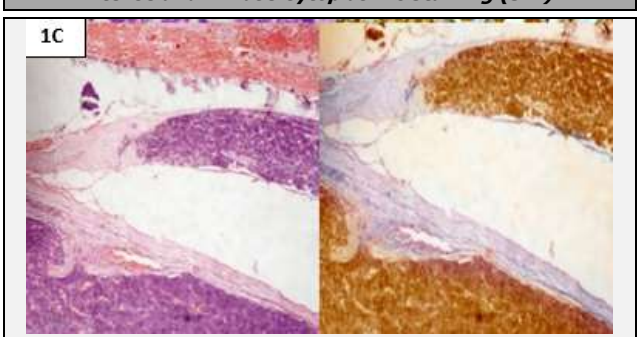

Figure 1C. H & E, 100X; Tumour Cells Arranged in Lobular Pattern with Focus of Capsular Infiltration. IHC Galectin-3, 100X ; Tumour Cells Showing Diffuse Staining (3 +)

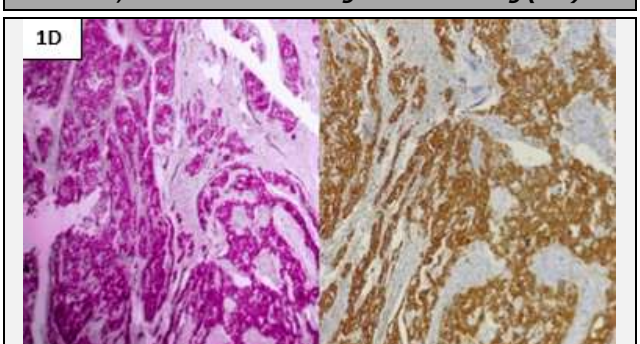

Figure 1D. H and E 100X - Showing Spindled Sarcoma Like Tumour Cells, IHC Galectin-3 : 100X : Tumour Cells Showing Intense and Diffuse Cytoplasmic Staining (3 +)

Of the six cases of FTC, 5 cases (83.33 %) were positive (3 +), (shown in Figure 1c) and one case (16.66 %) was focally positive (1 +). Of the two cases of Anaplastic carcinoma, both showed intense and diffuse staining (3 +) (shown in Figure 1d). One case each of Medullary carcinoma and Primary thyroid lymphoma showed negative staining.

Statistical significance of Galectin-3 expression in various lesions was compared and analysed using 2 X 2 contingency table. chi-square test with Yates correction was used to calculate P - value to ascertain statistical significance.

Lesion	No. of Positive Cases	No. of Negative Cases	P - Value
Benign	1 (5 %)	19 (95 %)	< 0.0001*
Malignant	30 (88.2 %)	4 (11.8 %)	

Table 1. Comparison of Galectin-3 Expression in Benign and Malignant Lesions

*indicates statistical association

With a statistically significant P-value (< 0.0001), the tendency of Galectin-3 expression was more in malignant neoplasms as compared to benign neoplasms.

Galectin-3 expression in malignant lesions was found to have a sensitivity of 88.23 %, specificity of 95.0 %, positive predictive value of 96.8 % and negative predictive value of 82.6 %

Lesion	No. of Positive Cases	No. of Negative Cases	P – Value
Follicular adenoma	1 (5.9 %)	16 (94.1 %)	0.018*
Follicular variant of Papillary carcinoma thyroid	2 (100.0 %)	0 (0.0 %)	

Table 2. Comparison of Galectin-3 Expression between Follicular Adenoma and Follicular Variant of Papillary Carcinoma Thyroid

*indicates statistical association

With a P-value of 0.018, that was statistically significant, the tendency of positive expression was seen to be more in follicular variant of papillary carcinoma thyroid than in follicular adenoma.

Lesion	No. of Positive Cases	No. of Negative Cases	P – Value
Follicular adenoma	1 (6.3 %)	15 (93.8 %)	0.001*
Follicular carcinoma	5 (83.3 %)	1 (16.7 %)	

Table 3. Comparison of Galectin-3 Expression between Follicular Adenoma and Follicular Thyroid Carcinoma

*indicates statistical association

With a statistically significant P-value (0.001), the tendency of Galectin-3 expression was more in follicular carcinoma as compared to follicular adenoma. Galectin-3 expression in follicular thyroid carcinoma was found to have a sensitivity of 83.3 %, specificity of 93.8 %, positive predictive value of 83.3 % and negative predictive value of 93.8 %.

DISCUSSION

A total of 54 consecutive thyroidectomy specimens received in the Department of Pathology, which were macroscopically and microscopically diagnosed as neoplasms were analysed in this study. Majority of cases were females accounting for 81.48 % and males accounted for 18.52 %. In a study conducted by Htwe et al. 82.6 % female cases and 17.4 % male cases were encountered.[3] In a study conducted by Pallavi et al. females constituted 78.4 % and males constituted 21.9 %.[4] Results of both the studies are in close approximation with the present study. Over 87 % of the cases were in the age group of 21 - 60 years and peak incidence was found in third decade of life. In a study by B S Sumana et al. 90 % of the thyroid neoplasms were in the age group of 20 - 60 years[5] and in a study done by Tsegaye and Ergete et al. 85.7 % of the thyroid lesions were found in the age group of 20 - 59 years.[6] Results of both studies are concordant with the present study.

Benign lesions accounted for 37.04 % of cases and malignant lesions accounted for 62.96 % of cases of all the neoplastic cases. Follicular adenoma was the most common benign neoplasm accounting for 31.48 % of all cases. Majority of patients of follicular adenoma were seen in 31 - 40 years of age. Similar observations were made in a study conducted by Ajay Kr et al.[7]

Amongst the malignant lesions studied, papillary carcinoma was the most common (71 %), followed by follicular carcinoma (18 %). Anaplastic carcinoma accounted for 6 %. Medullary carcinoma and primary thyroid lymphoma accounted for 3 % each. This was in concordance with results of studies conducted by Ajay Kr Singh et al.[7] Jaudah Al - Maghrabi et al.[8] and Pallavi et al.[4] The present study correlated well with study done by Ajay Kr Singh et al.[7] In this study increased incidence of papillary carcinoma was seen from second to fifth decade of life. This was in concordance with results of Pallavi et al.[4] and Shrikande et al.[9] Microscopically five variants of papillary carcinoma were identified including the classic variant. Two cases each of encapsulated and follicular variant, one case each of tall cell variant and microcarcinoma. Five cases of follicular carcinoma were encountered in the present study and all cases showed capsular and vascular invasion. Two cases of anaplastic carcinoma were encountered in the present study. A single case of medullary carcinoma and primary thyroid lymphoma were also encountered in the present study. Saxen et al.[10] found only 58 % agreement among five Nordic pathologists when tested the reducibility of WHO classification of thyroid tumours on 696 cases. A more recent study by Hirokawa et al. the agreement of benign versus malignant was encountered in only 62 % of the nodules, who had compared the diagnoses of 21 follicular nodules by four American and four Japanese pathologists.[11] In a review by Fassina et al. of 200 thyroid tumours, good agreement for papillary and anaplastic thyroid carcinomas, moderate for medullary and poor agreement for follicular thyroid carcinomas were encountered.[12]

In a more recent review of 41 follicular carcinomas by five experienced French thyroid pathologists, the agreement for malignancy varied from 5 % among all five pathologists to 56 % between two pathologists. It is clear from these studies and others that there is interobserver variation in the diagnosis of thyroid neoplasms.[13]

Galectin-3 immunohistochemical expression hence was used as an ancillary technique to aid in the accurate diagnosis of thyroid neoplasms. In a largest series reported by Bartolazzi et al. Galectin-3 positivity was found in 3 % of

follicular adenomas.[14] Park et al.[15] and Segura et al.[16] also found Galectin-3 positivity in a single case of follicular adenoma (3 % and 4.7 % respectively), which was in concordance with the present study (5 %).

Study	Follicular Adenoma	Classic variant - PTC	Follicular variant - PTC	Follicular carcinoma	Medullary carcinoma	Anaplastic carcinoma
Fernandez et al.[17]	0 %	100 %	-	50 %	50 %	100 %
Orlandi et al.[18]	-	100 %	100 %	100 %	-	-
Bartolazzi et al.[14]	3 %	97 %	-	95 %	43 %	90 %
Coli et al.[19]	-	100 %	100 %	60 %	-	100 %
Weber et al.[1]	30 %	92 %	-	44 %	-	-
Segura et al.[16]	4.7 %	100 %	-	81 %	-	-
Prasad et al.[20]	10 %	94 %	-	67 %	-	100 %
Jaudah al Maghrabi et al.[8]	31 %	92 %	-	60 %	-	-
B S Sumana et al.[5]	6 %	93 %	75 %	50 %	50 %	100 %
Pallavi et al.[4]	10 %	100 %	67 %	66 %	0 %	-
Present study	5 %	94.44 %	100 %	83.33 %	0 %	100 %

Table 4. Comparison of Galectin-3 Expression in Thyroid Neoplasms between Present Study and Other Studies

Galectin-3 was positive in 95.8 % of papillary carcinoma cases which was in concordance with a study by B S Sumana et al.[5] Prasad et al.[20] Jaudah al Maghrabi[8] and Weber et al.[1] who reported 93 %, 94 %, 92 % and 92 % Galectin-3 positivity in papillary carcinoma thyroid cases respectively. In various studies Galectin-3 positivity was identified in 82 % to 100 % cases of classic variant of papillary carcinoma.[21] In a study by Prasad et al.[20] Giannini et al.[22] and Bartolazzi et al.[14] Galectin-3 positivity in classic variant of papillary carcinoma thyroid was 94 %, 93 % and 97 % respectively which was in concordance with the present study (94.44 %). Galectin-3 expression in follicular variant of papillary carcinoma thyroid was noted in 100 % of cases (N = 2) which was in concordance with the studies by Barroeta et al.[23] Torres – Cabala et al.[24] Orlandi et al.[18] and Coli et al.[19] who reported 75 – 100 % Galectin-3 positivity in follicular variant of papillary carcinoma thyroid. Expression of Galectin-3 ranged from 20 % to 100 % in follicular carcinoma in various studies.[21] Orlandi et al.[18] and Segura et al.[16] in their studies reported 100 % and 81 % Galectin-3 positivity in follicular carcinoma cases which was in concordance with the present study (83 %). In the present study Galectin-3 expression was negative in medullary carcinoma thyroid which was concordant with the study of Pallavi et al.[4] In cases of anaplastic thyroid carcinoma, Galectin-3 positivity was noted in 75 % to 100 % of cases.[21] Both cases of Anaplastic thyroid carcinoma showed 100 % Galectin-3 positivity which was in concordance with the studies done by B S Sumana et al.[5] Prasad et al.[20] Coli et al.[19] and Fernandez et al.[17] Various studies have shown the ability of Galectin-3 to discriminate thyroid cancer from benign thyroid nodules.[15,25] Thus use of Galectin-3 expression represents a promising adjunctive test that aids in thyroid cancer diagnosis.

CONCLUSIONS

Amongst the 54 neoplastic thyroidectomy specimens analysed, the commonest benign lesion encountered was follicular adenoma and the commonest malignant lesion encountered was papillary carcinoma thyroid. Galectin-3 was highly expressed in thyroid cancer, but not in normal thyroid tissue and infrequently in benign thyroid lesions. To conclude Galectin-3 is useful as a sole marker in differentiating benign and malignant thyroid neoplasms ($P < 0.0001$). Among the follicular patterned lesions, Galectin-3 is sensitive for follicular variant of papillary carcinoma and follicular carcinoma. Thus Galectin-3 aids in thyroid cancer diagnosis and may also represent attractive target for therapy of thyroid cancers. Disaccharide methyl β – lactosaminide analogues are being evaluated for their ability to selectively block Galectin-3 binding to receptors. But available methodologies like IHC procedure and marker interpretation need to be standardized as it bears an impact on the accurate reporting of Galectin-3 expression in thyroid lesions. Thus Galectin-3 protein expression evaluated using immunohistochemistry technique acts as an adjunctive ancillary technique in thyroid cancer diagnosis.

Data sharing statement provided by the authors is available with the full text of this article at jebmh.com.
Financial or other competing interests: None.
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