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Histomorphological study of malignant thyroid neoplasm in a tertiary care center and evaluation of Galectin 3 expression in papillary thyroid carcinoma

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ABSTRACT

Galectin-3 is a beta-galactoside binding animal lectin, which is frequently associated with tumour progression and metastasis. In recent years, overexpression of Galectin-3 has been reported in various human cancers and more frequently in thyroid neoplasms. The aim of this study was to analyze the histomorphological characteristics of malignant thyroid neoplasms, subtype them according to the established classification system and to evaluate the expression of Galectin-3 immunostaining in papillary thyroid carcinoma. A total of 30 cases were included in the study, out of which 28 cases were papillary thyroid carcinoma and its variants and one case of medullary and anaplastic carcinoma. Majority of the papillary thyroid carcinoma cases were positive for Galectin 3 immunostaining (25/28 cases – 89%) in our study. We conclude that galectin-3 is consistently expressed in papillary carcinoma thyroid; however, there are few false-negative cases in this study and also other studies have reported Galectin 3 overexpression in non-papillary tumors. Hence, we cannot depend on Galectin 3 expression alone as a single diagnostic tool to detect papillary thyroid carcinoma.

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INTRODUCTION

Thyroid neoplasms encompass the majority of all endocrine neoplasms. They include a wide variety of benign and malignant lesions. Among the malignant tumors, papillary carcinoma is most common with a frequency of 70 to 85 % and preponderance among young females (Kunjumon and Upadhyaya, 2014; Al-Brahim and Asa, 2006). The diagnosis of papillary carcinoma is primarily based on the histomorphological examination, i.e., papillary architecture and nuclear features that include optical clearing, overlapping, nuclear grooves and pseudo inclusions. However, in cases with equivocal features, the diagnosis based on histomorphology alone can be quite challenging.

In general, when treated appropriately, papillary thyroid carcinoma has a good prognosis compared to other malignant tumors of the thyroid. Hence, it is critical to diagnose papillary carcinoma correctly for therapeutic purposes and for assessing the prognosis. In cases with equivocal histomorphological features, immunohistochemistry can be used as an adjunct to aid in the diagnosis. The present study aims to study the histomorphological features of malignant thyroid neoplasms and to evaluate the expression of immunohistochemical marker Galectin 3 in papillary thyroid carcinoma.

MATERIALS AND METHODS

This was a laboratory-based, retrospective study carried out at the Department of Pathology in Saveetha medical college and hospital, Chennai. The study period was from January 2018 to June 2019. Purposive sampling method was used. The samples were collected after ethical approval. A total number of 30 blocks, corresponding to the malignant thyroid neoplasms, were retrospectively retrieved using the unique histopathology numbers from the archives. Three to four-micron sections were taken from each of the blocks using Leica 2125RTS microtome. The sections were mounted on the H &E labelled slides. The slides were then stained by Harris haematoxylin and Eosin Staining. The H&E slides were evaluated by senior pathologists and the histomorphological characteristics of these neoplasms and their subtype according to the established classification systems were noted. Parameters such as age, sex, tumor size, lymph node status, etc. were noted from the archived data.

Two to four-micron sections were cut from each of the study blocks for Galectin 3 immunohistochemical staining. One positive and one negative control were included in each batch and were therefore subjected to the same test conditions as the study cases.

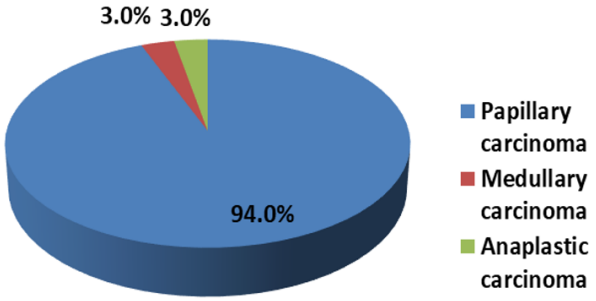

Figure 1: Distribution of malignant thyroid lesions

Interpretation of Galectin 3

Interpretation of galectin 3 expression was done according to the criteria defined by Orlandi *et al.* (1998) and Weber *et al.* (2004).

Positive Galectin 3 staining

was defined as the presence of nuclear staining or cytoplasmic staining of more than 30% of the tumour cells irrespective of the intensity of staining.

Negative Galectin 3 staining

was defined as an absence of any staining in the tumour cells or staining less than 30% of the tumour

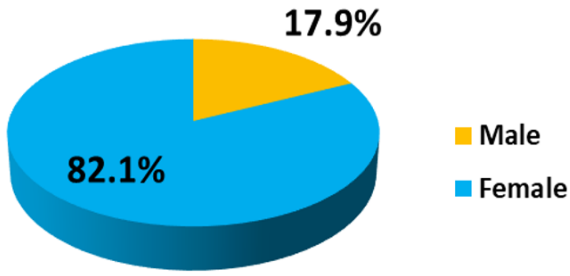

Figure 2: Sex distribution of papillary thyroid carcinoma

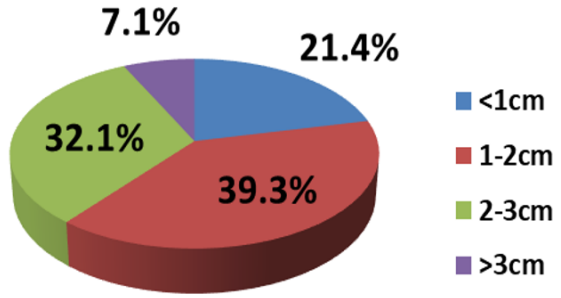

Figure 3: Tumour size in papillary thyroid carcinoma

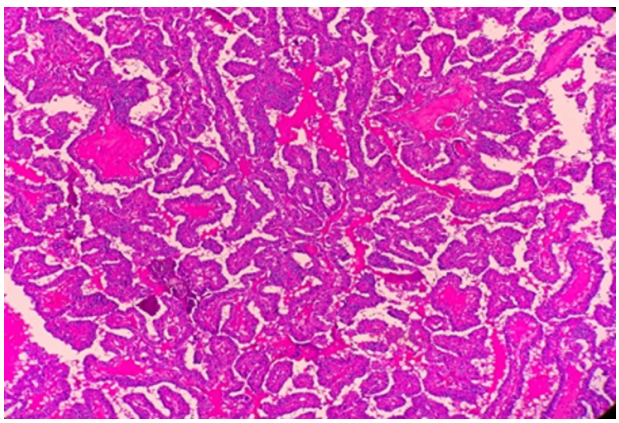

Figure 4: Low power view showing a case of papillary carcinoma - classical type

Table 1: Scoring the staining intensity for Galectin 3

Staining intensity of Galectin 3	Scores
No staining	0
Weak staining	1+
Moderate staining	2 +
Strong staining	3 +

Table 2: Scoring the proportion of cells stained

Percentage of cells stained	Score
0% of positive cells	No
1 – 30% of positive cells	1
31-60% of positive cells	2
61-100% of positive cells	3

Table 3: Age incidence of papillary thyroid carcinoma in other studies

	0 -10 years	11 – 20 years	21 – 30 years	31 – 40 years	41 – 50 years	51 – 60 years	61 – 70 years	71 – 80 years
(Beigh *et al.*, 2018)	12		38	32	21	15	5	3
(Rao *et al.*, 2017)	1		2	16	20	9	6	1
(Carcangiu *et al.*, 1985)	1	20	42	62	54	32	25	5
(Kishore *et al.*, 1996)	-	1	7	12	1	4	4	4
Present study	-	1	4	8	5	5	5	-

Table 4: Histological variants of papillary thyroid carcinoma

Diagnosis	No. of Cases	Percentage
Papillary micro carcinoma	6	21%
Papillary carcinoma - classical	20	72%
Papillary carcinoma – follicular variant	2	7%
Total	28	100%

Table 5: Regional lymph node involvement in papillary thyroid carcinoma cases

Regional lymph nodes	No. of Cases	Percentage
Involved	6	21.4%
Not involved	22	78.6%
Total	28	100%

cells irrespective of the intensity of staining.

Evaluation of the expression of Galectin 3 was performed as follows

Every lesion was given a score according to the intensity of the nuclear or cytoplasmic staining (Table 1) and the proportion of the neoplastic/ non neoplastic cells taking up the stain (Table 2). Immunohistochemical slides were screened by 2 pathologists for evaluating the proportion and intensity of the staining.

RESULTS AND DISCUSSION

The malignant thyroid lesions included in the study were comprised of 28 cases (94%) of papillary thyroid carcinoma, one case (3%) of medullary carci-

Table 6: Galectin 3 staining in variants of papillary thyroid carcinoma

			Galectin 3		Total
			Positive	Negative	
Diagnosis	Papillary micro carcinoma	Count	5	1	6
		% within Diagnosis	83.3%	16.7%	100.0%
	Papillary carcinoma – classical type	Count	19	1	20
		% within Diagnosis	95%	5%	100.0%
	Papillary carcinoma – follicular variant	Count	1	1	2
		% within Diagnosis	50%	50%	100.0%
Total		Count	25	3	28
		% within Diagnosis	89.3%	10.7%	100.0%

Table 7: Proportion of cells stained with galectin 3 in PTC

Proportion	No. of Cases	Percentage
0%	2	7.1%
1+ (<30% cells positive)	1	3.6%
2+ (30-60% cells positive)	18	64.3%
3+ (>60% cells positive)	7	25%
Total	28	100%

Table 8: Intensity of staining in PTC

Intensity	No. of Cases	Percentage
0	2	7.1%
1+	5	17.9%
2+	14	50%
3+	7	25%
Total	28	100%

Table 9: Galectin 3 expression among PTC cases in other studies

Source	PTC, NO. (%)
(Dunđerović *et al.*, 2015)	87/94 (92%)
(Barroeta *et al.*, 2006)	9/11 (82%)
(Park *et al.*, 2007)	179/181 (99%)
(Scognamiglio *et al.*, 2006)	47/49 (96%)
(Prasad *et al.*, 2005)	63/67 (94%)
(Rossi *et al.*, 2006)	37/42 (88%)
(Matos *et al.*, 2005)	61/84 (73%)
(Savin *et al.*, 2008)	126/147 (86%)
(Torregrossa *et al.*, 2007)	152/200 (76%)
(Saleh *et al.*, 2010)	18/20 (90%)
(Murphy *et al.*, 2008)	20/20 (100%)
Present study	25/28 (89%)

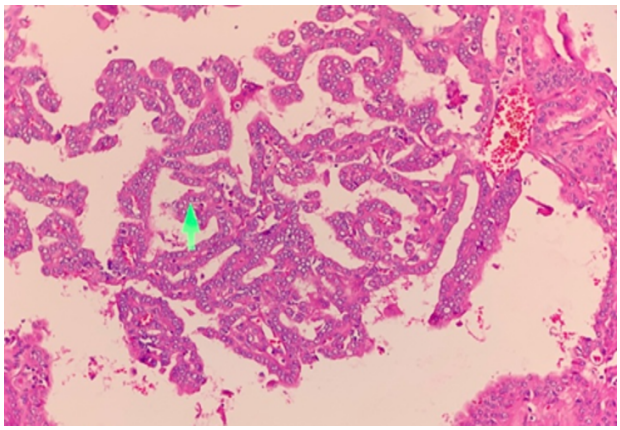

Figure 5: High power view showing a case of papillary carcinoma - classical type, arrow – nuclear grooving and optically clear nucleus

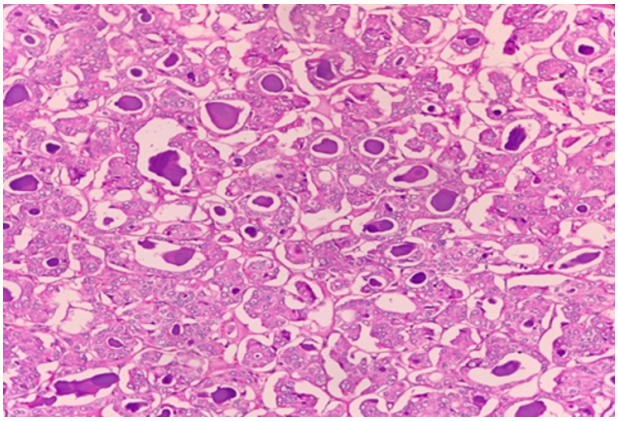

Figure 6: High power view showing a case of papillary carcinoma – follicular variant

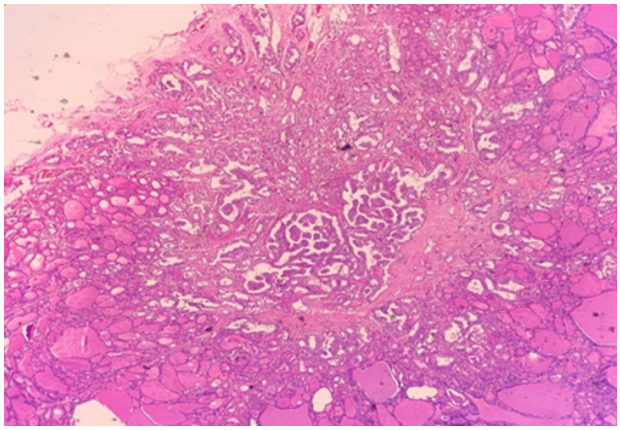

Figure 7: Low power view showing a case of papillary micro carcinoma

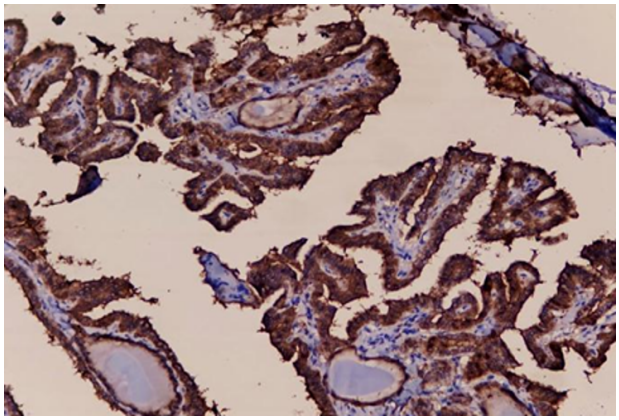

Figure 8: High power view showing intense (3+) cytoplasmic Galectin 3 staining in > 60% of the tumor cells in a case of PTC – classical type

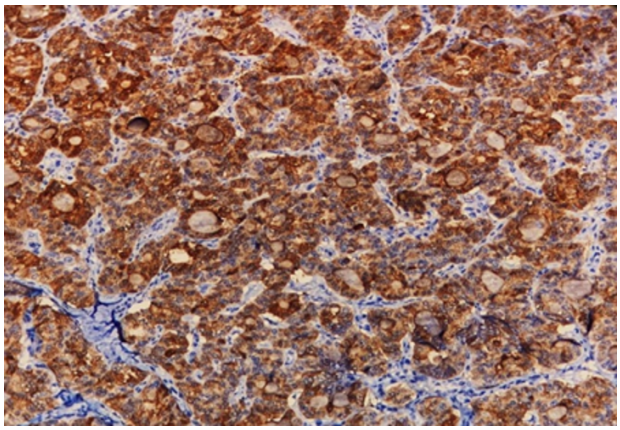

Figure 9: High power view showing moderate (2+) cytoplasmic Galectin 3 staining in > 60% of the tumor cells in a case of PTC – follicular variant

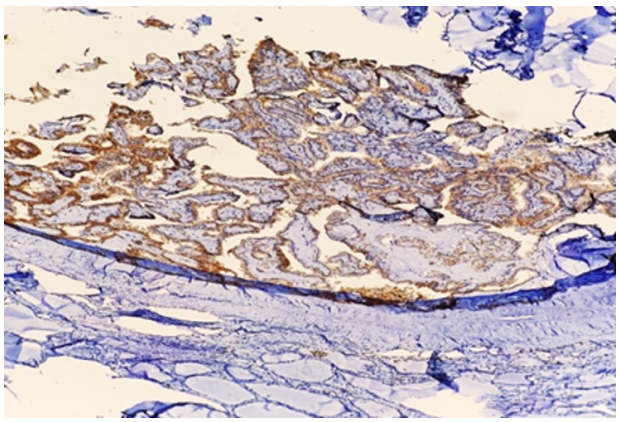

Figure 10: Low power view showing mild (1+) cytoplasmic Galectin 3 staining in 30 - 60% of the tumor cells in acase of PTC – micro carcinoma

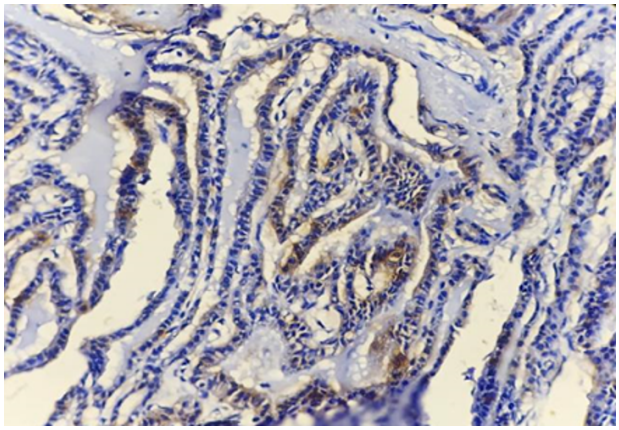

Figure 11: High power view showing mild (1+) cytoplasmic Galectin 3 staining in < 30% of tumour cells –considered negative for Galectin 3 in a case of PTC – classical type

noma and one case (3%) of anaplastic carcinoma (Figure 1). The majority of patients with PTC were between 31 - 40 years of age (39.3%) and 35.7% of patients were more than >50 years. The age incidence in other studies is compared in Table 3. Significant female predominance was noted in PTC, with a male to female ratio of 1:4.5 (Figure 2). This was in concordance with the previous literature and also with studies done by Carcangiu *et al.* (1985) and Beigh *et al.* (2018). In the present study, out of the 28 cases of papillary thyroid carcinoma cases, 20 were classic type (Figures 4 and 5) comprising 72% followed by Papillary micro carcinoma (Figure 7) - 6 cases (21%) and follicular variant (Figure 6) – 2 cases (7%) (Table 4). We did not receive other variants during our study period. This correlates with the study done by Shah (2015) with the predominance of a classic variant. The right lobe of thyroid was observed to be the most common site of PTC in our study. In the present study, we observed a mean tumor size of 1.8 cm (Figure 3), multifocality was seen in 32% of the PTC cases and 21.4% of cases had lymph node metastasis (Table 5), Rao *et al.* (2017) observed multifocality in only 8% of the PTC cases which was much less compared to our study and lymph node metastasis in 23.9% of cases. Lymphovascular invasion and extra thyroidal extension was noted only in a single case of PTC. The medullary and anaplastic carcinoma cases were unifocal, negative for LVI, extra thyroidal extension and lymph node metastasis. Majority of the papillary thyroid carcinoma cases were positive for Galectin 3 immunostaining (25/28 cases – 89%). All 3 variants of papillary carcinoma in this study had a single case with negative Galectin 3 immunostaining (Table 6). The majority of papillary carcinoma cases had 2+ (30-60% cells positive) proportion (64.3%) (Figure 10) and 25% of cases had 3+ proportion (>60% cells positive) (Figures 8 and 9, Table 7). One case showed mild Galectin 3 immunostaining in < 30% of the tumor cells (Figure 11). The maximum number of papillary carcinoma cases had 2+ intensity (50%) (Figure 9) and 25% of cases had 3+ intensity (Figure 8). 17.9% of the cases showed mild 1+ immunotaining (Figures 10 and 11) (Table 8). A case of PTC with lymph node metastasis and extra thyroidal extension showed intense 3+ Galectin 3 staining in > 60% of the cells in our study. Tang *et al.* (2016) reported higher rates of Galectin 3 postivity in PTC cases with regional lymph node metastasis compared to cases without lymph node metastasis and concluded that PTC cases with Galectin 3 overexpression were more prone for lymph node metastasis.

Most studies have reported Gal -3 positivity in 90% to 100% of papillary carcinoma cases (Table 9). Our study showed that Gal -3 expression was slightly lower (89%) compared to other studies.

Galectin 3 overexpression is also reported in other neoplastic and non-neoplastic lesions of thyroid. Savin *et al.* (2008) observed galectin 3 overexpression in 56% of follicular thyroid carcinoma. Galectin 3 is also noted to be overexpressed in few cases of follicular adenoma, Hashimoto thyroiditis and nodular hyperplasia. Dunđerović *et al.* (2015) observed overexpression of galectin 3 in 40.7%, 13.3%, 50% of follicular adenoma, colloid goiter and hurthle cell adenoma cases respectively. The diagnosis of papillary carcinoma does not routinely require immunohistochemistry. When this is performed, it is usually to establish the thyroid origin of a tumor at metastatic sites.

Another situation is the use of immunochemistry for the differential diagnosis of papillary carcinoma from other benign and malignant thyroid lesions. Markers such as HBME-1 (membrane immunoreactivity), galectin-3 (both nuclear and cytoplasmic immunoreactivity), cytokeratin 19 (cytoplasmic immunore activity), and CITED1 (both nuclear and cytoplasmic immunore activity) are frequently over expressed in papillary carcinoma. HBME-1, followed by galectin-3, is considered the most specific (Scognamiglio *et al.*, 2006). CD56 is typically negative in papillary thyroid carcinoma (Park *et al.*, 2009). The sensitivity and specificity of these markers were reported to be 87.5% and 83.6% (Galectin 3), 87.3% and 83.1% (HBME-1), 82.2% and 63.1% (CK 19) respectively (Liu and Lin, 2015). The sensitivity and specificity increases when these markers are used as a panel.

CONCLUSION

Histomorphological assessment remains the gold standard for the diagnosis of papillary thyroid carcinoma. However, in doubtful cases with equivocal morphology poses a great challenge in reaching an accurate diagnosis. In those cases, immuno histochemistry can be done to aid in the diagnosis. Though there is a significant association between Galectin 3 immunoreactivity and the diagnosis of papillary thyroid carcinoma, there are few false-negative cases in our study and other studies have shown Galectin 3 positivity in other non-PTC lesions. Hence we cannot depend on Gal-3 expression alone as a single diagnostic tool to detect papillary thyroid carcinoma.

There is no single immuno histochemical marker having 100% sensitivity or specificity for diagnosing papillary thyroid carcinoma. So instead of using a single marker, a panel of markers comprising of HBME-1, Galectin-3, CITED-1 and CD 56 can be used to improve the sensitivity and specificity.

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