Original Article

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Diagnostic Utility of Galectin-3 in Papillary Lesions of Thyroid

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Abstract

Introduction: Papillary thyroid carcinoma (PTC) is the most common malignant neoplasm of the neck. Most cases of PTC are diagnosed based on pathologic criteria. However, few thyroid lesions that mimic nuclear features or the architecture of PTC pose diagnostic problems. Papillary projections may be encountered in benign papillary hyperplasia of multinodular goiter, Hashimoto's thyroiditis, and Graves' disease. For this reason, the approach to these challenging lesions should include immunohistochemistry. Galectin-3(Gal-3) is an immunohistochemical marker that shows positivity in PTC. The present study was undertaken to investigate whether strong galectin-3 expression is an essential hallmark of PTC or papillary thyroid hyperplasia.

Material and Methods: Gal-3 expression was sought by immunohistochemistry in 33 cases of papillary patterns (on microscopy) of thyroid specimens received at our institution. The results obtained were statistically analysed.

Result and Conclusion: Of the 33 cases studied, 17 were PTC, and 16 were papillary hyperplasia. Immunohistochemical stain with Galectin -3 revealed a statistically significant P – value, which proves the tendency for Galectin -3 expression is higher in PTC than in papillary hyperplasia.

***Keywords**: Galectin- 3, Immunohistochemistry, PTC, Papillary thyroid hyperplasia*

Introduction

The most common malignant tumor of all the thyroid gland malignancies is papillary carcinoma of the thyroid (PTC), which accounts for 85% of all thyroid cancers. [1] Histopathology is the gold standard for the diagnosis of PTC. However, few lesions pose potential diagnostic difficulty due to the presence of papillary fronds with fibrovascular core and nuclear pleomorphism. [2] For this reason, the approach to these lesions must include immunohistochemistry (IHC) besides microscopy. [3] Several studies were done to evaluate IHC markers to distinguish benign from malignant thyroid lesions. However, very few Indian studies are documented. The present study sought Gal-3, a carbohydrate-binding protein, to differentiate PTC from other mimickers.

Material and methods

A cross-sectional study was carried out on thyroidectomy specimens which showed papillary patterns on histopathology at the Department of Pathology from 1st December 2015 to 30th June 2017 after getting an ethical approval from the Ethical Committee of our institution and written informed consent was obtained as well. Immunohistochemistry with Gal-3 antibody was done, and slides were examined and photographed at 100X and 400X. The percentage of positive cells was evaluated by counting number of positively stained cells in 10 high power fields for each specimen and graded using a 0-3 scoring system. (Table-1) [4]

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Result

Out of 33 cases, PTC was slightly higher compared to that of cases of papillary hyperplasia. The age distribution of the cases in our study was in the age group of 10-60 years. The Distribution of cases by papillary hyperplasia and PTC are shown in Table-2.

Discussion

The thyroid gland is affected by a heterogeneous group of lesions manifested by varied histomorphology patterns,

which can produce diffuse or nodular growth. [5] PTC is the most common histologic type of thyroid gland carcinoma showing follicular cell differentiation with distinct and characteristic nuclear features. However, these microscopic features are not pathognomonic for PTC; thus, they must be differentiated from other mimickers as it has an excellent long-term prognosis if appropriately diagnosed and treated. [6]

Table 1: Immunohistochemical scoring pattern (0-3 scoring system) [4]

Score	Staining intensity	Proportion
0	No staining	-
1+	Slight staining	<5% of cells
2+	Moderate staining	5% -25% of cells
3+	Intense staining	>25% of cells

Table 2: Distribution of cases by Papillary hyperplasia and PTC

Diagnosis	Diagnosis	N	Percent
Papillary hyperplasia	Colloid cyst	1	3.0
	Cystic nodular goitre	6	18.2
	Graves' disease	1	3.0
	Hashimoto's thyroiditis	1	3.0
	MNG	7	21.2
	Total	16	48.5
PTC		17	51.5

Table 3: Distribution of Gal-3 immunostaining in our study

Gal-3	Negative		Positive		p-value
Diagnosis	N	Percent	N	Percent	
Papillary hyperplasia	14	87.5	2	12.5	<0.001*
PTC	2	11.8	15	88.2	
Total	16	100.0	17	100.0	
*significant difference at a 5% level of significance					

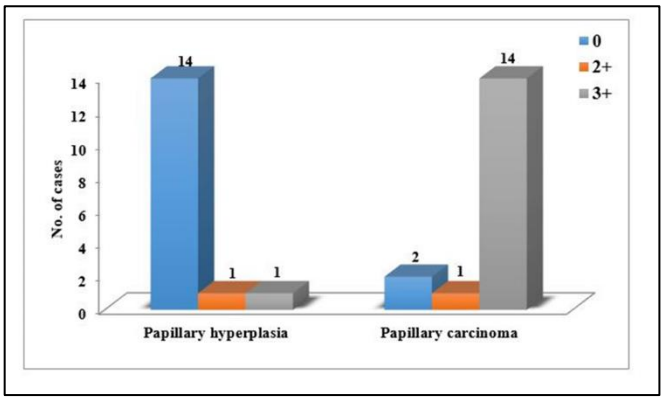

Figure 1: Distribution of Gal-3 immunostaining in our study

The presence of papillae alone is not a pathognomonic feature of PTC. Papillae are seen in many other non-neoplastic and neoplastic lesions like multinodular goitre (MNG), thyrotoxicosis, congenital errors of thyroid metabolism, Hashimoto's thyroiditis, follicular adenoma (FA), medullary carcinoma, hurtle cell adenoma, and hurtle cell carcinoma. So, they must not be confused with PTC. [5,6]

Hypertrophy of the follicular cells and hyperplasia lead to infolding, which appears as papillations. The architecture of papillae is different in various thyroid lesions. The main important feature to distinguish diffuse papillary hyperplasia from PTC is the preservation of gland architecture in the former. [5]

Predominantly papillae in PTC are arborizing with delicate fibrovascular cores, few papillae can also be broad with oedematous, fibro cellular, or hyalinised and lined by tumor cells showing characteristic nuclear features of PTC. Follicles varying in size and contour are present, containing darkly stained colloid. [5]

The papillae in thyrotoxicosis, FA, and Hashimoto's thyroiditis are short, non-branching, and protrude into the follicular lumen without a true fibrovascular core. The diffuse nature of papillae also points towards the non-neoplastic nature of the lesion. Whereas papillae in nodular goitre and FA with papillary hyperplasia are predominantly extremely oedematous, haemorrhagic, and broad, comprised of thyroid follicles in the core, and few delicate branching papillae are present which are lined by regular, columnar cells without crowding, basally placed round nuclei without clearing in a 'beads on a string' fashion. The absence of psammoma bodies is also characteristic. [5,6]

Pseudo papillae with 'rugged surfaces' are seen in medullary carcinoma of the thyroid due to cellular dehiscence. A few papillae are also noted in hurtle cell adenoma, and hurtle cell carcinoma, which is non-arborizing, and lining cells do not show crowding. Occasionally, the lining cells show nuclear grooves, inclusions, and calcified colloid mimicking psammoma bodies.

Most cases of papillary hyperplasia of Graves' disease can be easily distinguishable from papillary carcinoma based on the histologic and cytologic features. But few cases of Graves' disease may simulate papillary carcinoma. Histologic features which simulate malignancy are well-developed papillary fronds with fibrovascular cores and large vesicular nuclei. Other histologic features which help

to differentiate are the preservation of gland architecture, nuclear cytology, lack of stromal desmoplasia, and psammoma bodies. However, the distinction between these may be difficult. [7]

Hence, in addition to histopathology, additional ancillary methods are required to distinguish papillary hyperplasia from PTC. Studies done in the past by Hirokawa *et al*, [8], Franc B *et al* [9], and Fassina *et al* [10] revealed that there exists inter-observer variation in the diagnosis of thyroid neoplastic lesions. Hence immunohistochemistry is helpful for the diagnosis of thyroid lesions.

Gal-3 is one such marker, its immunohistochemical expression is used to aid in accurately diagnosing thyroid neoplasms. Like the literature, in the present study, on microscopy, papillary patterns were noted in cases of nodular goitre, colloid cyst, Graves' disease, Hashimoto's thyroiditis, PTC, and its variants.

In the current study, papillary carcinomas showed a higher incidence in females than males. Similarly, the studies done by Heitz *et al* [11] and Shrikhande *et al* [12] noted a higher incidence of papillary carcinoma in females, with female to male ratios of 3.1:1 and 1.9:1, respectively.

In the study done by Sapio M R *et al*, [13] 27.4% (17/62 cases), including nodular hyperplasia (15/51 cases) and FA (2/11 cases), showed positivity for Gal-3, whereas, in cases of PTC, 91.9% showed positivity for Gal-3, out of which classical variant of PTC cases comprised 78.9%. The sensitivity, specificity, PPV, and NPV of Gal-3 were 70.8%, 73.9%, 73.9%, and 70.8%, respectively.

Similarly, in a study done by Beesley *et al*, [14] predominantly papillary hyperplasia was noted in MNG, and FA showed negativity for Gal-3.

In the study by Mary *et al* [2] where Gal-3 immunohistochemical staining was done to differentiate between papillary hyperplasia and PTC. 93.3% of cases of papillary hyperplasia showed no expression or rare expression, and 6.6% of cases showed moderate expression. Whereas in cases of Papillary carcinoma, moderate to strong diffuse staining was seen in 80% of cases. 20% of cases showed rare positivity, resulting in a sensitivity and specificity of 100% and 40%, respectively.

Similarly, in our study, 87.5% of papillary hyperplasia cases displayed no staining for Gal-3 (Figure-2), whereas moderate and strong positivity was noted in 6.25% of cases each. However, 82.35%, 5.88%, and 11.7% cases of papillary carcinoma showed strong, (Figure-3) moderate, and weak positivity for Gal-3, respectively.

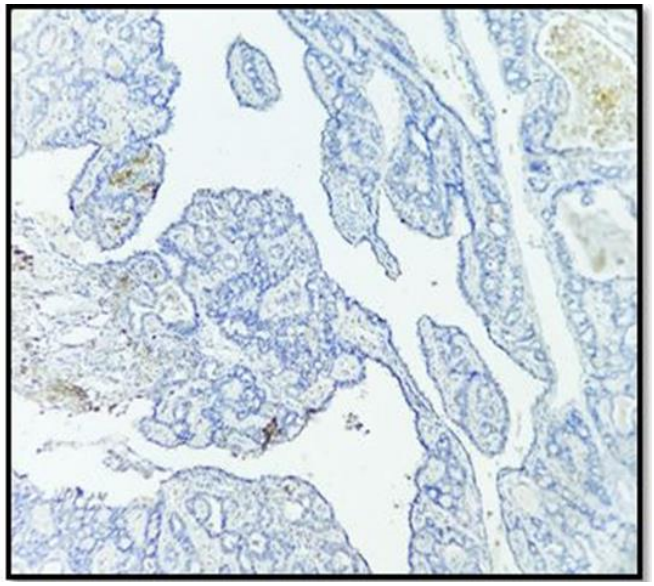

Figure 2: Papillary hyperplasia displayed no staining for Gal-3

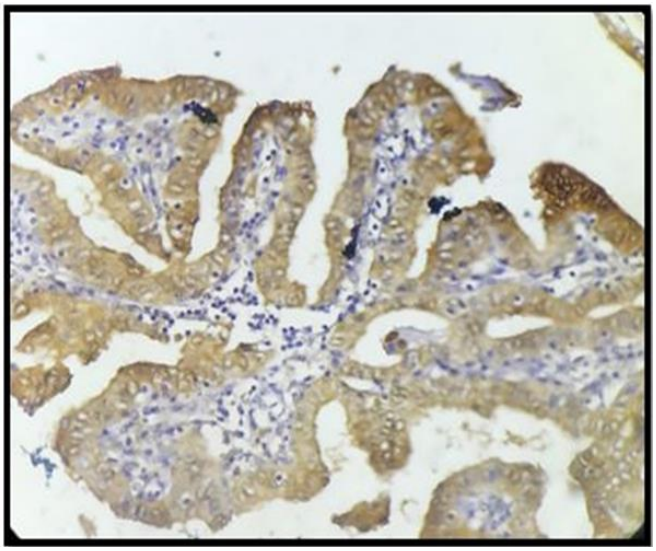

Figure 3: PTC showing strong Gal-3 positivity

Several studies have shown the ability of Gal-3 to discriminate PTC from other thyroid lesions [14-16]

Few of the studies in the past done by Prasad *et al* [17] showed frequent Gal-3 expression in benign thyroid lesions and in several non-thyroidal cells including fibroblasts and inflammatory cells, making it a marker with high sensitivity but lower specificity.

The presence of Gal-3 positive cells has been associated

with the presence of macrophages in benign nodular goitre and hurtle cells in adenomas. However, in the present study, Gal-3 expression showed striking differences between papillary hyperplasia and papillary carcinoma, like the studies done by other workers.

The Sensitivity, Specificity, Positive predictive value, and negative predictive value of Gal-3 expression to differentiate PTC from papillary hyperplasia are mentioned in Table-4.

Table 4: Sensitivity, Specificity, Positive predictive value (PPV) and negative predictive value (NPV)

Sensitivity	**88.24%**
Specificity	87.50%
PPV	88.24%
NPV	87.50%
Accuracy	87.88%

The results thus obtained in our study indicate that Gal-3 helps differentiate benign from malignant lesions of the thyroid gland.

Many studies with various combinations of immunohistochemical markers have been done. In these studies, specificity values increased, but sensitivity values decreased in comparison with single marker values.

Immunopositivity for Gal-3, HBME-1, and CK19 in the diagnosis of differentiated thyroid carcinoma has a sensitivity of 85.9 % and specificity of 100 %. The immune panel comprised of p16, ERK, and RET has 51% sensitivity and 89% specificity for carcinoma. However, out of all the markers used, the best immune panel consists of HBME-1, GAL-3, and CK19, with high sensitivity (54%) and specificity (100%). [18] In the various studies reviewed, the expression of Gal-3 in the classical variant of PTC ranged from 82% to 100% of the cases, like the present study as stated in Table-5.

Table 5: Positivity of PTC cases by Gal-3

S. No	Study	PTC Classic variant positivity (%)
1	Coli [19]	100%
2	Bartolazzi[20]	97%
3	Weber [21]	92%
4	Present study	88.2%

Conclusion

Most PTC cases can be diagnosed based on histopathologic criteria. Although histopathology is a gold standard for diagnosing PTC, few cases can mimic the morphology of PTC and can lead to misdiagnosis. Hence IHC is an essential and valuable adjunctive ancillary technique for these cases.

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