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Original Research Article

Role of p27 in differentiating follicular adenoma and follicular carcinoma of the thyroid

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ABSTRACT

Background: Thyroid neoplasms represent a broad spectrum of tumors with different biologic behaviour. Although investigations like thyroid function tests, scintigraphy and ultrasonography were routinely used for the diagnosis of thyroid nodules, they could not discriminate between benign and malignant lesions. The present study is undertaken to assess the expression of cell cycle protein such as p27kip1 (p27) in thyroid neoplasms which might be useful in predicting behaviour of various thyroid neoplasms and aid in their diagnosis. Aim of the study was to assess the expression of p27 and its role in differentiating follicular adenoma and follicular carcinoma of the thyroid.
Methods: The present study was undertaken to evaluate the expression of p27 in thyroid neoplasms with the help of immunohistochemical analysis over a period of 1 year. The study was conducted on archival blocks retrieved from the Department of Pathology, SMCH. 19 thyroid neoplasms were diagnosed (7 benign, 12 malignant) and IHC expression of p27 was studied.
Results: There was over-expression of p27 staining in case of follicular adenoma whereas malignant lesions showed underexpression on p27 staining. P27 expression was significantly different in follicular adenoma and follicular carcinoma of the thyroid.
Conclusions: The role of p27 in differentiating benign and malignant thyroid neoplasms may prove it to be a candidate marker if combined with other additional investigations like radionuclide scan or using a broad panel of IHC markers. This may provide more insight into the behaviour of tumors in a detailed manner.

Keywords: Follicular adenoma, Follicular carcinoma, Overexpression, p27, Underexpression

INTRODUCTION

Thyroid lesions are common among the general population and often represent a large proportion of endocrine referrals. It is convenient to divide the thyroid lesions, despite their large number, into two major categories: those showing a diffuse pattern such as hyperplasia and thyroiditis and those that produce nodules. Thyroid neoplasms represent a broad spectrum of tumors with different biologic behaviour. Although investigations like thyroid function tests, scintigraphy and ultrasonography were routinely used for the diagnosis of thyroid nodules, they could not discriminate between benign and malignant lesions.[1] The majority of them, however, can be readily diagnosed by characteristic histopathologic features. Recent studies with immunohistochemical markers have also been undertaken for evaluation of these thyroid lesions. These markers have been studied in normal tissues, as well as in benign and malignant tumors with the hope of finding significantly different values among these groups that could be exploited diagnostically.

The present study is undertaken to assess the expression of cell cycle protein such as p27kip1 (p27) in thyroid neoplasms, which is inhibitory in nature and might be useful in predicting behaviour of various thyroid neoplasms and aid in their diagnosis.

Tumor suppressor gene p27 is located on chromosome 12p13. It encodes the CDK inhibiting nuclear protein. It inhibits the formation of cyclinD1/cdk complexes during G0 and early G1 phases of the cell cycle.[2] Normal thyroid follicular cells show strong immunoreactivity for p27 on immunohistochemistry, whereas p27 expression is reduced in both hyperplastic and neoplastic thyroid nodules. P27 levels have been reported to be lower in neoplastic nodules compared with hyperplastic nodules, in malignant tumors compared with benign tumors, and in poorly differentiated carcinomas compared with well differentiated carcinomas.[3-7] Aim of the study was to assess the expression of p27 and its role in differentiating follicular adenoma and follicular carcinoma of the thyroid.

METHODS

The present hospital based prospective study was undertaken in the Department of Pathology, Silchar Medical College and Hospital, Silchar, expression of p27 in thyroid neoplasms with the help of immunohistochemical analysis over a period of 1 year (June 2019 to May 2020). 19 thyroid neoplasms were diagnosed (7 benign, 12 malignant). Therefore, immunohistochemistry with p27 was done on the 19 neoplasms as per IHC protocol.

Inclusion criteria

Histopathological examination performed as a diagnostic procedure in thyroid swelling will be included.

Exclusion criteria

Swellings in front of neck other than thyroid swelling and patients with bleeding disorders was excluded.

All data were collected, compiled and subjected to suitable statistical analysis. For statistical analysis Chi-square test and Fisher's exact test were used. A p value of less than 0.05 was considered statistically significant. The statistical software SPSS Version 20 was used for the analysis of the data and Microsoft Office word and Excel 2007 have been used to generate graphs, tables etc.

Histopathological examination

Thyroid resected specimens were fixed in 10% formalin and brought to the laboratory. Detailed gross examination was done and recorded systematically. The specimens were then sectioned from representative areas followed by H and E staining and IHC. Antibody to p27 (Monoclonal Mouse antibody, Clone DCS72, 6ml/RTU, Biogenex). The positive control taken in the study was normal thyroid tissue with very strong nuclear positivity. The negative control used were sections of the study tissues with no primary antibody incubation.

IHC Interpretation

For p27

p27 expression was assessed on the intensity of nuclear staining within tumor cells.[8] Again cytoplasmic staining or immunoreactivity displayed by fibrovascular , stromal and lymphoid cells was not considered. The intensity of staining was graded 0 to 4 as follows.[8,9] Grade 0: total absence of staining; grade 1: faint nuclear staining (requiring high power assessment); grade 2: moderate nuclear staining (easily appreciated); grade 3: strong nuclear staining (but noticeably less than normal); grade 4: staining as strong as normal thyroid tissue. Underexpression was defined as a grade 0-1 staining.

Quantitation of p27 immunoreactivity was based on the prevalent intensity of staining within the tumor. Tumors displaying a uniform intensity of staining throughout the tumor, quantitation was straightforward. For the occasional tumor with heterogenous expression, p27 immunoreactivity was graded according to the intensity displayed by the majority of tumor cells.[8]

RESULTS

Considering age and sex incidence, thyroid swelling was common in 3rd and 4th decade of life and showed a female predominance. Age of the patients ranged from 6 to 66 years with a median age of 35 years. Mean age was 35.24 years with a standard deviation of 13.43 years. Malignant thyroid lesions accounted for 12 out of which FTC accounted for 3 cases; 2 female and 1 male. All the swellings were solid in consistency. FA included 7 cases, 4 female and 3 male. All of them were solid in consistency.

p27 expression in thyroid neoplasm

p27 expression was studied in all 19 cases of thyroid neoplasm. There was over-expression of p27 staining in case of follicular adenoma whereas malignant lesions showed underexpression on p27 staining (Table 1).

Table 1: p27 expression in thyroid neoplasms.

p27 status	number
Overexpression	7
Underexpression	12
Total	19

Among the thyroid neoplasms, high p27 expression was seen in 7 cases (all follicular adenoma) while low p27 expression was seen in 12 cases of malignant thyroid

lesion. The difference was statistically significant (p=0.0001).

Table 2: p27 expression in different histological types of thyroid neoplasms.

Malignancy	Overexpression of p27	Underexpression of p27
Papillary Thyroid Ca (PTC)	0	6
Follicular Thyroid Ca (FTC)	0	**3**
Medullary Ca of Thyroid (MCT)	0	2
Anaplastic Ca (AC)	0	1
Follicular Adenoma (FA)	7	0

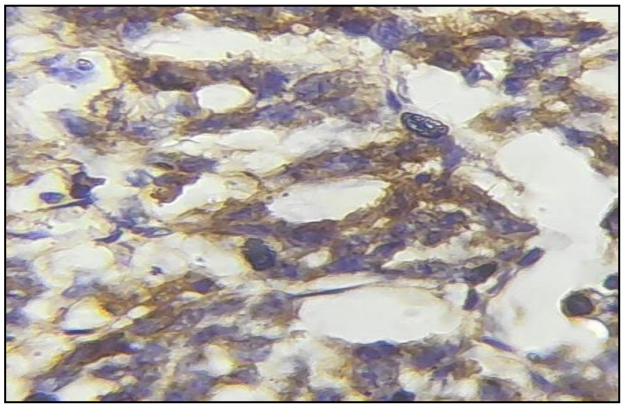

Figure 1: P27 expression (grade 3) in another case of follicular adenoma (10x).

p27 expression in different histological types of thyroid neoplasm. Overexpression of p27 was seen in all 7 cases of FA while underexpression was noted in all 3 cases of FCT. The difference was statistically significant (p=0.0027). Thus p27 assay can help to differentiate between FA and FCT (Table 2).

DISCUSSION

Age distribution

Most of the patients in this study were in the age group of 20-29 years. Studies conducted by Golder et al, Monika Modi et al, Hossain MM et al stated that the peak age range of presentation in their study was 21-40 years.[8,11,12]

Sex distribution

There is a significant female preponderance in our study, which is very much in accordance with the studies of Modi et al, Solomon et al, Kahmke et al.[11,13,14]

Immunohistochemistry

There was a significant difference in the expression of p27 between FA and FTC (p=0.027) which is in accordance with the studies by Temiz et al and Erickson et al.[3,15] Also we found a highly statistically significant correlation (p=0.0001) among p27 expression among the thyroid neoplasms. p27 showed overexpression in all cases of FA and underexpression in all malignancies.

Resnick et al in their study of 87 benign and malignant thyroid lesions found that all of the thyroid neoplasms examined exhibited significantly lower p27 expression than did normal thyroid tissue (P<.001).[6] Poorly differentiated carcinomas had the lowest p27 staining frequency of all carcinomas examined. p27 staining frequency of the papillary carcinomas was significantly lower than that of the follicular carcinomas (p<0.001). The follicular variant of papillary carcinoma had a significantly higher p27 staining frequency (p=0.05) than did classical papillary carcinoma.

Erickson et al noted that there were significant differences in the expression of p27 between follicular adenomas (labeling index (LI)=47.9±5.6) and follicular carcinomas (LI=15.7±2.0) and p27 was effective in distinguishing follicular adenomas from follicular carcinomas (p=0.0056).[3] Zhang et al found p27 to be the most frequent single positive marker consistent with benign nature of most indeterminate thyroid nodules.[16] Abulkheir et al noted that p27 immunohistochemical results were significantly different between follicular adenomas including those with atypical features and minimally and widely invasive follicular carcinomas with highly statistically significant difference.[17]

CONCLUSION

For most thyroid tumors, histopathological examination alone can reach to a diagnosis. However, in some cases, the pathologist is confronted with thyroid lesions that are difficult to diagnose as benign or malignant and such lesions include mostly the follicular- patterned lesions (eg. FA, FTC, FVPTC, Oncocytic variant of PTC etc). IHC may prove to be a beneficial ancillary test in the follicular-patterned thyroid tumors. In our study, we have taken p27, (cell-cycle inhibitor) to study it's role in the diagnosis of follicular adenoma and carcinoma which is difficult by histopathology alone. It's role in differentiating benign and malignant thyroid neoplasms may prove it to be a candidate marker if combined with other additional investigations like radionuclide scan or using a broad panel of IHC markers.

This may provide more insight into the behaviour of tumors in a detailed manner. However, a peek into the clinical significance of such markers in patients of thyroid malignancies has to be further defined by prospective studies with larger sample sizes and wide

spectrum of lesions which might help in providing a more accurate, scientific and clinically relevant consultation.

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REFERENCES

1. Taneri F, Poyraz A, Salman B, Tekin E, Arkyuerek N, Bayram O, et al. Using imprint and frozen section in determining the surgical strategies for thyroid pathologies. Endocrine Regulations. 2001;35:71-4.
2. Wang S, Wuu J, Savas L, Patwardhan N, Khan A. The role of cell cycle regulatory proteins, cyclin D1, cyclin E, and p27 in thyroid carcinogenesis. Hum Pathol. 1998;29:1304-9.
3. Erickson LA, Jin L, Wollan PC, Thompson GB, van Heerden J, Lloyd RV. Expression of p27kip1 and Ki-67 in benign and malignant thyroid tumors. Mod Pathol.1998;11:169-74.
4. Lloyd RV, Jin L, Qian X, Kulig E. Aberrant p27kip1 expression in endocrine and other tumors. Am J Pathol. 1997;150:401-7.
5. Erickson LA, Yousef OM, Jin L, Lohse CM, Pankratz VS, Lloyd RV p27kip1 expression distinguishes papillary hyperplasia in Graves' disease from papillary thyroid carcinoma. Mod Pathol. 2000;13:1014-9.
6. Resnick MB, Schacter P, Finkelstein Y, Kellner Y, Cohen O. Immunohistochemical analysis of p27/kip1 expression in thyroid carcinoma. Mod Pathol. 1998;11:735-9.
7. Liu W, Asa SL, Fantus IG, Walfish PG, Ezzat S . Vitamin D arrests thyroid carcinoma cell growth and induces p27 dephosphorylation and accumulation through PTEN/Akt-dependent and -independent pathways. Am J Pathol. 2002;160:511-9.
8. Kim DH, Lee HI, Nam ES, Shin HS, Sohn JH, Park CH, et al. Reduced expression of the cell-cycle inhibitor p27Kip1 is associated with progression and lymph node metastasis of gastri carcinoma. Histopathology. 2000;36:245-51.
9. Troncone G, Laccarino A, Russo M, Volante M, Papotti M, et al. Accumulation of p27(kip1) is associated with cyclinD3 overexpression in the oxyphilic (Hurthle cell) variant of follicular thyroid carcinoma. J Clin Pathol. 2007;60:377-81.
10. Golder S, Satpathy SN, Padhy RK, Panigrahi R, Ghata S. A clinicopathological study of solitary thyroid nodule. J Pharm Biomed Sci. 2015;05(03):233-7.
11. Modi M, Daveshwar M. Study of histopathological pattern of thyroid lesions. Int J Biomed Advance Research.2018;9(1):27-36.
12. Hossain MM. Surgical management of thyroid diseases: a study on 78 cases. Mymensingh Med J. 2002;11(1):628.
13. Raphael S, liyasul I, Mohammed AZ. Histopathological pattern of thyroid lesions in Kano, Nigeria: a 10-year retrospective review (2002-2011). Nigerian J Basic Clin Sci. 2015;12(1):55-60.
14. Kahmke R. Utility of intraoperative frozen sections during thyroid surgery. Int J Otolaryngol. 2013;8:75-9.
15. Temiz P, Akkas G, Nese N, Duman FU, Karakas C, Erhan Y. Determination of apoptosis and cell cycle modulators (p16, p21, p27, p53, BCL-2, Bax, BCL-xL, and cyclin D1) in thyroid follicular carcinoma, follicular adenoma and adenomatous nodules via a tissue microarray method. Turk J Med Sci. 2015;45:865-71.
16. Zhang L, Krausz T, May RM. A pilot study of Galectin-3, HBME-1, and p27 triple immunostaining pattern for diagnosis of indeterminate thyroid nodules in cytology with correlation to histology. Appl Immunohistochem Mol Morphol. 2015;23(7):481-90.
17. Abulkheir A, Hussein IL, Bilal D. Value of immunohistochemical expression of p27 and galectin-3 in differentiation between follicular adenoma and follicular carcinoma. Applied Immunohistochemistry Molecular Morphology. 2012;20(2):131-40.

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