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RESEARCH ARTICLE

IMMUNOHISTOCHEMICAL EVALUATION OF KI-67 IN PAPILLARY THYROID CARCINOMA AMONG SUDANESE PATIENTS

[1]Sahwa Omer Gorashi khogaly and [2,*]Esam Mohamed Abdelrahim Suliman

[1]Medical Laboratory Science, Neelain University, Khartoum, Sudan
[2]Associate professor Consultant Pathologist, Department of Pathology, College of Medicine and Health Sciences, Kassala University, Eastern Sudan

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ABSTRACT

Background: Papillary carcinoma of the thyroid gland (PTC) constitutes the most common form of thyroid cancer and the most common endocrine malignant tumor. It is often difficult to differentiate PTC from benign papillary hyperplasia of the thyroid gland based on their morphology. Cell proliferative activity is one of the important factors for assessing the biological behavior of carcinoma. At present, the most useful marker to evaluate cell proliferative activity is Ki-67, which is expressed in all cells except those in the G0 phase.
Objective and Design: Main objective of this retrospective cross-sectional descriptive study was to evaluate immunohistochemical expression of ki-67 in thyroid cancer especially papillary type among Sudanese patients.
Material and Methods: A total of 60 paraffin-embedded formalin-fixed tissue specimens from thyroid lesions were included in thisstudy and stained by H&E and immunohistochemistry.
Results: About 83.3% of the cases expressed Ki-67 (most of them were PTC) while only 16.7% of the cases were negative (P value is statically significant $p<0.002$).
Conclusion: It can be concluded that using of Ki- 67 as a diagnostic marker is helpful in diagnosis of papillary thyroid carcinoma.

INTRODUCTION

Thyroid cancer is the most common endocrine malignant tumor; papillary thyroid carcinoma (PTC) is the commonest form of thyroid cancer worldwide (about 80% of thyroid cancer) (DeVita *et al*., 2008). PTC, however, must be differentiated from follicular adenoma and follicular variant of PTC, because of close resemblance of some morphological criteria (Lloyd *et al*., 2004; Nikiforov *et al*., 2009). In recent years, a large number of molecular alterations in thyroid cancer have been used in the distinction of malignant from benign thyroid lesions. These biomarkers, such as CK19, TG, Ki67, Calcitonin, TTF-1, BRAF, RET, HBME-1, and galectin-3, have been translated into clinical practice which offered significant improvement in the preoperative diagnosis of thyroid cancer (Vierlinger *et al*., 2011; Magro *et al*., 2011; Chiu *et al*., 2010; Barut *et al*., 2010). Ki-67, a nuclear non histone protein, is synthesized at the beginning of cell proliferation, and it is expressed in all phases of the cell cycle except during G0 phase.

Corresponding author: **Esam Mohamed Abdelrahim Suliman,**
Associate professor Consultant Pathologist, Department of Pathology, College of Medicine and Health Sciences, Kassala University, Eastern Sudan.

Its strict association with cell proliferation and its co-expression with other well-known markers of proliferation indicate a pivotal role in cell division. Ki-67 expression has been widely used in clinical practice as an index to evaluate the proliferative activity of lymphoma. Many relevant literature have reported strong expression of Ki-67 in many malignant tumors (Sethi *et al*., 2010; Kato, 2009; Nikiforov, 2011; Fryknäs *et al*., 2006). In this study, we evaluated the immunohistochemical marker Ki- 67 and its diagnostic significance for papillary thyroid carcinoma in Sudan.

MATERIALS AND METHODS

This retrospective cross sectional descriptive study was conducted at Khartoum state, capital of Sudan, and included sixty formalin- fixed paraffin- embedded tissue blocks of thyroid cancer. These samples were taken from histopathology department at Ribat National University and Sahiroon Hospital. All tissue sections were stainedfirst with H & Eto confirm the diagnosis found in the records. Another 3-micrometer sections on salinized slides (Dako)were stained immunohistochemically to detect presence or absence of Ki-67 in tissues.

Immunohistochemical staining was achieved using streptoavidin-biotin immunoperoxidase technique (thermo fisher). Immunohistochemistry procedure was done as follows: sections were deparaffinized in xylene, rehydrated through graded series of alcohol (absolute – 90% -70%) and then placed in running water. Samples were steamed for antigen retrieval for Ki-67 using PT link. Endogenous peroxidise activity was blocked with peroxidase blocking reagent (3% hydrogen peroxide with methanol) into 10 mints. The slides were then incubated with 100 – 200 microliter of a monoclonal anti ki67 antibody ready to use (thermo-fisherDako) for 20 mints in a moisture chamber at room temperature and then rinsed in Phosphate Buffer Saline (PBS) for 3 minutes. Binding of antibodies was detected by the thermo Envision System(Dako – Envision TM Flex kit). Finally, sections were washed in three changes of PBS, followed by adding 3, 3 diaminobenzidine tetra hydrochloride (DAB; Dako) as a chromogen to produce the characteristic brown stain for the visualization of the antibody/ enzyme complex for up to 5 min. Slides were then counterstained with haematoxylin and allowed to air dry and them cover -slipped with permanent mounting media. Negative controls, in which the primary antibodies were replaced by PBS, were carried out for each primary antibody. For Ki-67, known PTC slides were used as positive internal control. Data were analyzed using computer SPSS program version 18 software for analysis of the study data. Results were presented by using frequencies, percentages and means. Chi-square test was used to study the correlations between Ki-67 expression and the histological subtypes of tumors. P-value was considered significant when < 0.05.Ethical consideration was fulfilled from scientific committee of Neela in University and Khartoum Hospital.

RESULTS

Frequency of thyroid lesions in this study is shown in the following table (table number 1).

Type of Lesion	Frequency	Percentage
Papillary Carcinoma	50	84
Follicular Adenoma	5	8
Hashimoto's Thyroiditis	5	8
Total	60	100

Positive expression of Ki-67 was found in 45 cases (75 %); they were as follows: 42 cases of papillary thyroid carcinoma, 2 cases of follicular adenoma, and one case of Hashimoatos thyroiditis. Negative expression of Ki-67 was found in 15 cases (48.3%), that is shown in table number 2.

Table 2 shows the frequency of expression of Ki-67 in among study population

Histological Diagnosis	Positive Ki-67 expression	Negative Ki-67 expression	Total
Papillary Carcinoma	42	8	50
Follicular Adenoma	2	3	5
Hashimoto's Thyroiditis	1	4	5
Total	45	15	60

P value for expression in papillary carcinoma was significant ($p<0.002$).

DISCUSSION

Despite many advances in management of thyroid nodules and cancer by using fine needle aspiration cytology (FNAC) and cytological assessment, searching of the reliable and repeatable immune his to chemical markers for the distinction between benign thyroid nodules and papillary thyroid carcinoma seems to be continuous. In this study, most of the positive expression of Ki-67 in thyroid lesions was noticed in papillary carcinoma of the gland. Several studies worldwide agreed with this result (Cattoretti *et al*., 1992; Saiz *et al*., 2002; Choudhury *et al*., 2011; Ito *et al*., 2010; Tan *et al*., 2011). However, as the number of patients in this study is relatively small (60 patients), more precise results can be obtained from larger numbers representing the whole population.

Conclusion

Using Ki-67 as a diagnostic marker is helpful in reliable diagnosis of papillary thyroid carcinoma, so it can be recommended that Ki-67 marker must be included in routine thyroid diagnostic profile in Sudan.

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