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Expression of CK19 in papillary thyroid carcinoma in comparison with benign thyroid lesions

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Abstract

Background: The Papillary variant of thyroid carcinoma is one of the common types of thyroid malignancies , the commonest. Its diagnosis usually is microscopic which based on nuclear features .
Objective: To assess the immunohistochemical expression of cytokeratin 19 (CK19) in PTC and compare its reactivity with other thyroid conditions to approve its importance as a useful test for diagnosing PTC.
Patients and Methods: Twenty- cases of papillary thyroid carcinoma (with different variants), five follicular adenomas and ten multinodular goiters (MNG) were collected over three years (2018-2021).10% formalin-fixed sections were collected from thyroidectomy specimens. Stained with Hematoxylin and eosin then immunohistochemical staining for immune-marker CK 19 was done using standard techniques. The results were quantitatively scored as the following: score 0 (negative), score 1+ (<5%) positive cells), score 2+ (5- 25%), score 3+ (25-75%) ,finally score 4+ (>75%) positive cells), and then calculated.
Results: An 18 (90%) papillary carcinomas show diffuse and strong (3+ and 4+) expression of CK19 . ,three out of ten (30%) MNG were weakly positive(1+ and 2+) and focal in distribution while in follicular adenoma all cases were negative for CK19 .
Conclusion: Ck 19 can stain benign and malignant thyroid tissue, but strong membranous staining applied in cases of papillary ca , thus can be used as confirmatorytool for PTC diagnosis.
Keywords: Cytokeratin 19, thyroid, papillary thyroid carcinoma, immunostaining , histopathology, MNG

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Introduction

Papillary thyroid carcinoma (PTC) is the most common type (80-93%) of thyroid carcinomas [1] , characterized by the nuclear features , such as change of nuclear size; nuclear enlargement, change in nuclear shape with overlapping in addition to chromatin margination and clearing [2]. Nuclear membrane changes include irregular nuclear membrane, a nuclear grooving with nuclear pseudo inclusion [3]. There are Fifteen variant of papillary thyroid carcinoma, one of them is the classic papillary thyroid types , as stated in the 2017 WHO classification [4].

Due to the widely available and safety usage of ultrasound, there is increment in the diagnosis of papillary thyroid carcinoma in the last 25 years due to early diagnosis of thyroid nodules by radiological tools like

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(ultrasound and CT), which is called the thyroid cancer epidemics ; most of them at early stages [6].

Nearly all thyroid disorders including PTC are of female predominance with Female : male ratio of 3 to 1 [7].

At the microscopic level, the most common microscopic variant are classic PTC, micro-carcinoma, follicular type of papillary ca [8].

Occult (subclinical) tumors can be found in 6% at autopsy (<10 mm), 46.6% can be multicentric, and 14% present with nodal metastasis [8].

Occult tumors are usually with male predominance [7].

Diagnosis of papillary thyroid ca is typically reached by using pre-operative fine needle aspiration cytology based on the finding of the typical uclear features.

The Molecular study of cytological aspirates may assist in the preoperative diagnosis of the malignancy [10].

Diagnosis of thyroidectomy specimen again based on finding the nuclear features, including alteration of nuclear size, and shape, alteration in chromatin (clumping) and nuclear membrane irregularity (groove and inclusion) [10] as shown in the following Figure (1).

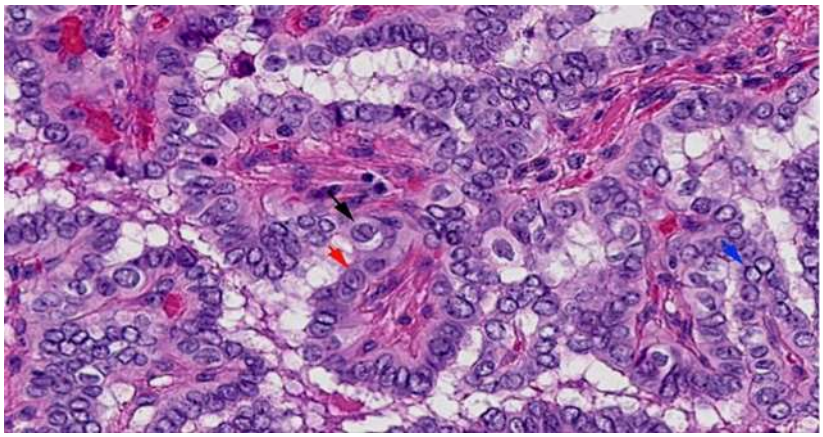

Figure (1): Show the microscopic feature of papillary thyroid ca like nuclear groove (black arrow), ground glass nucleus (blue arrow), and psuedoinclusion (red arrow)

There are many antibodies (immunohistochemical stains) available that are positive for thyroid cells like .Cytokeratin AEI\AE3, CK7, TTF1PAX8, and thyroglobulin . BRAF is positive test for PTC [10]. The utility Of CK19 to differentiate malignant from benign ones remains not clearly defined [11,12,13].

Other specific immunohistochemical stains include CDX2 ; used for the columnar cell variant (+ve in 50% of cases [14] and Ki67 index if more than 10% with aggressive tumors with high recurrence rate [15].

Patients and Methods

In this descriptive retrospective study a total of Thirty- Five cases of excisional thyroid biopsies were collected over 3 years from 2018 to 2020. The cases were already diagnosed by Hematoxylin-eosin stain and retrieved from the archive of AL-Shaheed Ghazi AL-Hariri Hospital. After that the immuno_histochemical stains were applied on 5-µm-thick paraffin sections on negatively

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charged slides. A Primery antibody for CK19 was applied for each section .

Positive control : ductal breast cells. Negative control ; Hepatocytes (as recommended by the leaflet). Evaluation of staining : positive staining of CK19 considered when a membranous and/or cytoplasmic staining pattern of cells with brown color.

Expression t of CK19 staining was quantitatively scored as shown in the following [16].

Table (1): Show the semiquantitative scoring of CK19 antibody in to five scores according to the number of cells taking stain [16]

No. of + stained cells	Score of CK19
No cells	0
< 5	1+
5-25	2+
25-75	3+
➢ 75	4+

Statistical Analysis

The included data in this study were statistically calculated according the proportions, percentage , ratio and range methods by using 2007 window program.

Results

Forty-five patients with recurrent inguinal Clinicopathological Analysis : Thirty- five cases of thyroidectomy were included in this retrospective study.Their age was ranging from 27-55 y with the most frequent age (50%) were in the 3rd decade of life . Regarding patients sex ; male to female ratio was (1:1.4). The predominant microscopic type was papillary thyroid ca , usual type (15) case, (42%) , follicular variant of ca was 5 (14%) , follicular adenoma was 5 (14%), and multinodular goiter 10 cases (28%) .

Correlation between CK19 and type of tumors : in this descriptive study , the majority of cases were of PTC that all show high scores (3+, 4+) of positivity as mentioned in this Table (2), Figure (2) other lesions present with focal and patchy expression or negative one.

Table (2): The expression of CK19 in different thyroid lesions with intense expression in cases of papillary thyroid ca and the least score 0 in benign goiter and follicular adenoma

CK19 score	No. of cases	Microscopic type
0	12	6 multinodular goiter , 5 follicular adenoma 1 PTC
1+	4	4 multinodular goiter
2+	4	PTC
3+	6	PTC
4+	9	PTC

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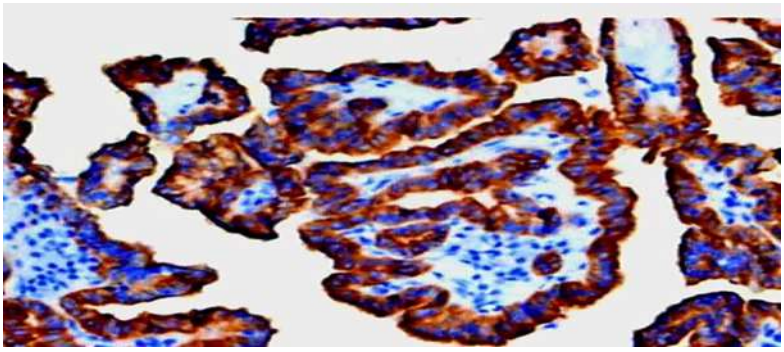

Figure(2): Showing the intense membranous expression of CK19 in papillary thyroid ca. score 4+

Figure(3): Showing the negative expression of CK19 in follicular adenoma , score 0

Correlation between CK19 and patient age : there is no correlation between age and CK19 score. Correlation between CK19 and sex of the patients : results show there is good correlation between sex and score. High score cases were with female , which is the largest group in PTC patients. Correlation between the sex and histopathological type: results show there is increasing in the malignant types of thyroid lesions (PTC) in females rather than males.

Discussion

Gender distribution : in this retrospective study , we found that are all types included in our studywere of femalepredominance . the male\female ratio (1\1.4) which go with Rebecca L Siegel *et al* [16] in which there is 3 : 1 female to male ratio despite the higher NO. of patient used by them. Also compatible with Karrissa LeClair *et al* eho search for subclinical cases was 14% in women and 12% in males from the total subclinical thyroid lesion at autopsy [17] , but there is no correlation between CK19 expression and sex of patients.

CK19 in benign lesions: the he types of benign diseases included in this study were the follicular adenoma and multinodular goiters due to their microscopical variation including papillary and micropapillary features , the expression of the immunohistochemical stain CK19 was negative in the majority of cases (7) which represent 50% of the non-malignant cases and 50% were weakly positive (score 1+ , 2+). These results agree with the study of Noroozinia et al that show CK19 negative in most cases of follicular adenoma [18].

CK19 in malignant lesions ; the results of our study show positive CK19 expression

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and the malignant nature of thyroid lesions specifically PTC (75%) with diffuse and intense expression , (20%) with focal positivity , and only (5%) negative which may be due to technical errors. Which are the same result done by Asmaa Gaber abdou *et al* in which there is 92.9 % positivity to CK19 in PTC cases , with most follicular adenomas were negative [19] . In the study of Suna Arkilic MD ; all the cases of PTC were diffusely and intensly positive for CK19 , while the cases of follicular adenoma and multinodular goiter were negative and aminority of 8% stained positive [20].

The results of John N Flanagan *et al* strengthen our study by confirming all cases of PTC intense and diffuse membranous staining in CK19 with negative stainingin multinodular goiter [21].

Conclusions

1. CK19 expression in 95% of studied PTC cases with various score of expression (2+__4+) .
2. The expression of CK19 was 100% negative in follicular adenoma and focal , patchy in some cases of multinodular goiter.
3. CK19 can be used to determine the benign from the malignant thyroid diseases.
4. There is positive correlation between patients sex and CK19 score.

Recommendations

The present study suggests that CK19 is a good useful marker for confirmation diagnosis of papillary thyroid carcinoma at the microscopic level.

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Ethical clearance: Ethical approval was obtained from the College of Medicine / University of Diyala ethical committee for this study.

Conflict of interest: Nil

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التعبير المناعي للدالة CK19 في الاورام الحلميه الخبيثه للغدة الدرقيه ومقارنتها مع الاورام الحميده

ذرى عباس فاضل [١]

الملخص

خلفية الدراسة: تعتبر الاورام الحليمية الخبيثة للغده الدرقية من اكثر الاورام شيوعا فيها ويعتمد تشخيصها على المواصفات والتغيرات المجهرية في النواة.

اهداف الدراسة: لبيان التعبير المناعي للدالة CK19 في الاورام الخبيثة الحلمية للغدة الدرقية ودراستها في الاورام الحميده والمقارنة بينهم وامكانية استخدام الداله في تشخيص هذا النوع من السرطانات.

المرضى والطرائق: عشرون حاله من اورام الغدة الدرقية الحلمية تشمل خمسة اورام جريبية و عشرة اورام عقدية و جمعت طوال ثلاث سنوات من الارشيف الخاص بمختبرات مستشفى الشهيد غازي الحريري للجراحات التخصصية . النماذج الماخوذه كانت مشخصه مسبقا من قبل اخصائيي المستشفى وتم اعادة صبغها بالصبغه الروتينيه وثم صبغها بالداله المناعية CK19 وتم حساب النتائج وفق التالي : بلاصبغه (٠)، اقل من ٥% (رقم ١)، من ٥-٢٥% رقم(٢)، من ٥٠-٧٥%(رقم٣) واكثر من ٧٥% (رقم٤).

النتائج: وجدنا ١٨ حاله اي مايقارب ٩٠% من الورم الحليمي للغده الدرقية اظهروا صبغه قويه لل ck19 رقم (٣و٤)،ثلاثة من اصل عشرة حالات للورم العقدي اظهروا صبغه متوسطه رقم(١و٢) واخيرا الورم الجريبي الحميد لم يظهر ايه استجابه للداله المناعيه.

الاستنتاجات: الداله المناعيه CK19 ممكن ان تصبغ الحالات السرطانية والحميدة للغده الدرقية بدرجات متفاوتة ولكن الصبغه تكون قوية في حالات سرطان الغده الدرقية الحليمي لذلك ممكن ان تستخدم في التشخيص النهائي للمرض.

الكلمات المفتاحية: الداله المناعيه CK19 ، الغده الدرقية، السرطان الحليمي ، الفحص النسيجي ، التعبير المناعي، الورم العقدي

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