

Immunohistochemical Expression of Cytokeratin 19 in Patients with Papillary Thyroid Carcinoma and its Mimics in Erbil, Kurdistan Region, Iraq

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Abstract

Background and objective: Papillary thyroid carcinoma (PTC) is the most common primary thyroid cancer. PTC diagnosis is based on the presence of classic nuclear features in most cases. However, there are some mimics including both benign neoplastic and non-neoplastic lesions, therefore immune-histochemical stains are necessary for equivocal cases. This study aimed to evaluate the diagnostic expression of CK19 in different thyroid lesions and also to differentiate PTC from other mimicking thyroid lesions.

Methods: A retrospective study of 90 cases of different thyroid lesions (56 patients with benign neoplastic and non-neoplastic lesions and 34 PTC) was investigated from January 2018 to January 2020. Immunohistochemical staining with CK19 was performed.

Results: CK19 IHC expressed in about 94% of PTC cases as moderate and strong pattern of staining, while in benign neoplastic and non-neoplastic thyroid lesions only 7% expressed as moderate and non with strong pattern of staining, it showed a significant statistical difference ($P < 0.001$). The sensitivity and specificity of CK19 total estimated score for diagnosis of PTC were 94.1% and 92.9%, respectively.

Conclusion: Although no single immunohistochemical marker is completely sensitive in differentiating benign from thyroid malignancy, this study found a significant and effective role of CK19 in distinguishing PTC from benign neoplastic and non-neoplastic mimickers' lesions. In addition, lymph node metastatic tumor cells retained the same staining intensity of CK19.

Keywords: Papillary thyroid carcinoma; Benign thyroid lesions; Immunohistochemistry; CK19.

Introduction

Papillary thyroid carcinoma is the predominant form of malignant thyroid neoplasm in countries with sufficient iodine diets.¹ It arises from epithelial follicular cells with distinctive architecture and nuclear features.² The gold standard method for diagnosis of papillary thyroid carcinoma is the pathological examination through routine hematoxylin and eosin stain (H&E). The presence of nuclear features such as nuclear overlapping, optically clear nuclei, nuclear grooves, and pseudo inclusions. In addition to papillary architecture and the presence of psammoma bodies, area diagnostic clue of PTC.³ However, the focal

morphologic overlap of such features in other thyroid lesions causes a diagnostic dilemma, and distinction from PTC becomes difficult. In such cases, immunohistochemical studies aid in the diagnosis of these problematic cases. Cytokeratin 19 is a low-molecular-weight about 40 kDa (smallest cytokeratin), found in both simple and complex epithelium, both normal and their neoplastic counterparts, normal follicular epithelium of thyroid gland showed no expression of CK19.⁴ The diagnosis of papillary thyroid carcinoma, including papillary microcarcinomas (smaller than 1 cm) incidentally found at surgery, is straight

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forward in most cases. However, some mimics, including follicular adenoma, goitrous nodules, and autoimmune thyroiditis including both Graves' disease and Hashimoto thyroiditis, show nuclear features or papillary architecture and growth pattern of PTC, creating diagnostic problems. On the other hand, some variants of PTC did not show typical or prominent nuclear features, therefore immunohistochemical studies help in the differentiation of PTC from mimickers.^{5,6} This study aimed to evaluate the diagnostic expression of CK19 in different thyroid lesions and also to differentiate PTC from other mimicking thyroid lesions.

Methods

A retrospective study of 90 surgically removed formalin-fixed, paraffin-embedded thyroid lesions was selected from the pathology department of PAR private hospital from January 2018 to January 2020. Demographic data (age at diagnosis and sex) and the topography of the tumor (location, pathological type of tumor, size, nodal status, and stage) were obtained from all patients. All the blocks were examined and the one which represented the tumor best (no necrosis, not much mesenchymal tissue) was selected for the study, and new sections were made and stained with Hematoxylin and Eosin (H&E) for evaluation. The staging was performed according to American Joint Committee on Cancer (AJCC) and the Union international center le cancer (UICC), by grouping the various TNM components, as T1-T2 and T3-T4. The research was approved by the Scientific and Research Ethics Committee of the University (code number HS-M 22-4).

The 90 selected thyroid lesions included:

a- 34 PTC cases.

17 follicular adenoma cases.

b- 8 cases of autoimmune thyroiditis, including Hashimoto's thyroiditis and Graves' disease.

c- 21 cases of nodular and multi-nodular hyperplasia or colloid goiter.

Method of immunohistochemical staining:

Labeled polymer and enhanced polymer system (DakoEnVision™ Flex) method according to Dako recommendation was used to stain tissue by Anti-CK19 antibody. The instruments used in IHC staining were Manual microtome, Dako PT Link, DakoAutostainer Link 48, and Olympus Bx22 Light microscope

1- 4mm thin sections were cut using a microtome and mounted on salinized slides.

2- A working solution was prepared by diluting the EnVision™ FLEX target retrieval solution in distilled water (dilution 1:50).

3- To cover the tissue section, the PT Link tanks were filled with a sufficient quantity (1.5L) of working solution

4- The PT Link was set to pre-heat the solution to 65C, then sections were immersed into the pre-heated EnVision™ FLEX Target Retrieval Solution (working solution) in PT Link tanks and incubated for 20-40minutes at 97C.

5- The Autostainer slid rack with the slides were removed from PT Link Tank and immediately dipped into a jar with diluted, room temperature EnVision™ FLEX Wash Buffer(20x) for 1-5minutes then the slides were placed in a DakoAutostainer Link 48.

6- The staining steps and incubation time were preprogrammed into the software of DakoAutostainer Link 48, were substrate Buffer EnVision™ FLEX peroxidase blocking reagent (as endogenous enzyme block), FLEX Anti CK19.

7- The staining steps and incubation times are pre-program into the software of DakoAutostainer link 48, were substrate buffer, EnVision™ FLEX Peroxidase blocking reagent (as endogenous enzyme block), flex anti CK19 (as a primary antibody), EnVision™ FLEX+ Mouse linker (as secondary reagent), EnVision/HRP (as labeled polymer, DAB+ Chromogen (as substrate Chromogen), EnVision™ FLEX Hematoxylin

(as counter stain) and distal water were applied on the slides.

8- Then slides were removed from the Autostainer link 48 and put graded ethanol (70%, 100%, 2x2x2 minutes) respectively, then in xylene (2 minutes).

9- The slides were mounted in Canada Balsam (organic solvent-based permanent mounting medium) and examined under a light microscope.

CK19score measurement:

Immunoreactivity for CK19 was assessed by the investigator. Membranous ± cytoplasmic staining was considered positive for CK19, only cytoplasmic positivity was infrequently encountered and was considered an artifact.

A semi-quantitative four-step scoring system (0-3) was used based on the staining intensity of the tumor tissue: 0 = negative; 1 = weak positive; 2 = intermediate positive; 3 = strong positive. CK19 positive refers to scores 1-3 and

CK19 negative to score 0.^{7,8,9} Normal skin (Squamous epithelium, basal layers) was used as a positive control for CK19, for negative control samples, the primary antibody was omitted for each run.⁸

A Mouse Monoclonal Anti-Human CK19, Clone RCK108, Ready-to-Use (DakoAutostainer/Autostainer. Plus).

Statistical Analysis:

Data were analyzed using the statistical package for social sciences (SPSS, version 25). Categorical variables were presented in the form of frequencies and percentages, while numerical variables were summarized in the form of means and standard deviations (SDs).

The Chi square test of association was used to compare proportions. McNemar test was used (in the 2X2 table) when the results of CK19 tests were compared with the histopathological examination (of the same patients); as in the following table:

		Histopathology			P (By McNemar)
		Carcinoma	Benign		
CK19	Positive	TP	FP	TP+FP	
	Negative	FN	TN	FN+TN	
Total		TP+FN	FP+TN	Grand total	

TP=True positive; TN=True negative; FP=False positive; FN=False negative. Sensitivity = TP / (TP+FN)*100; Specificity = TN / (FP+TN)*100; Predictive value positive (PV⁺): TP / (TP+FP) * 100; Predictive value negative (PV⁻): TN / (FN+TN) * 100; Total agreement = (TP + TN) / Grand total. A P value of ≤ 0.05 was considered as statistically significant.

Results

Ninety thyroid specimens were obtained in which divided into 56 benign neoplastic and non-neoplastic lesions and 34 patients of papillary thyroid cancer.

The mean age ± SD of patients with non-papillary thyroid lesions was 43.55 ± 15.12 years, and half of the patients were aged less than 40 years. The majority (82.1%) of them were females. Regarding the

histopathological type, more than one-third (37.5%) had nodular & multi-nodular hyperplasia or goiter, 32.1% had autoimmune thyroiditis, and 30.4% had follicular adenoma (Table 1).

Table 1 Clinico-pathological characteristics of non-papillary thyroid lesions

	No.	(%)
Age (years)		
< 30	9	(16.1)
30-39	19	(33.9)
40-49	12	(21.4)
50-59	9	(16.1)
60-69	4	(7.1)
≥ 70	3	(5.4)
Mean (±SD)	43.55	(±15.12)
Gender		
Female	46	(82.1)
Male	10	(17.9)
Histopathological type		
Follicular adenoma (FA)	17	(30.4)
Autoimmune thyroiditis (AIT)	18	(32.1)
Nodular & multinodular hyperplasia or goiter	21	(37.5)
Total	56	(100.0)

It is evident in Table 2 that the mean age \pm SD of patients with papillary thyroid cancer was 45.47 ± 18.57 years, and half of them were aged less than 40 years. More than two-thirds (70.6%) of carcinoma patients were females. The type of operation was mostly (67.6%) total thyroidectomy.

Different sizes were detected, ranging from ≤ 1 cm to more than 4 cm. The lymph nodes were involved in three patients (8.8%) only. Regarding the focality, it was single in 64.5% of the carcinoma patients and multifocal in 35.5% (Table 2).

Table 2 Clinico-pathological characteristics of papillary thyroid cancer cases

	No.	(%)
Age (years) n = 34		
< 30	9	(26.5)
30-39	8	(23.5)
40-49	5	(14.7)
60-69	8	(23.5)
≥ 70	4	(11.8)
Mean (\pm SD)	45.47	(± 18.57)
Gender (n = 34)		
Female	24	(70.6)
Male	10	(29.4)
Type of operation (n = 34)		
Total thyroidectomy	23	(67.6)
Right or left thyroid lobectomy	8	(23.5)
A known case of PTC with positive lymph node	3	(8.8)
Size (n = 31)		
≤ 1 cm	8	(25.8)
1.1-2 cm	11	(35.5)
2.1-4 cm	6	(19.4)
> 4 cm	6	(19.4)
Microscopical diagnosis (n = 34)		
Papillary thyroid carcinoma (PTC)	31	(91.2)
Lymph node involvement by papillary thyroid carcinoma	3	(8.8)
T stage (n = 31)		
T1a	7	(22.6)
T1b	11	(35.5)
T2	7	(22.6)
T3	6	(19.4)
Lymph node status (n = 31)		
No LN	5	(16.1)
Positive LN N1	6	(19.4)
Regional lymph nodes cannot be assessed Nx	20	(64.5)
Focality (n = 31)		
Single	20	(64.5)
Multifocal	11	(35.5)

It is evident in Table 3 that about 94% of the cases of thyroid papillary carcinoma showed either moderate or strong staining of CK-19, about 6% revealed weak staining and none of them had no staining, while for the benign neoplastic and non-neoplastic thyroid lesions about 32% showed no

staining, about 61% showed a weak pattern, about 7% showed moderate and none showed strong staining ($P < 0.001$). The rate of thyroid carcinoma in the whole sample was 37.8%, as presented in Table 4.

Table 3 Immunohistochemical staining for CK-19 in various thyroid lesions

	No staining	Weak	Moderate	Strong	p^*
	No. (%)	No. (%)	No. (%)	No. (%)	
Papillary thyroid carcinoma	0 (0.0)	2 (6.5)	14 (45.2)	15 (48.4)	
Lymph node involvement by papillary thyroid carcinoma	0 (0.0)	0 (0.0)	1 (33.3)	2 (66.7)	
Follicular adenoma	6 (35.3)	9 (52.9)	2 (11.8)	0 (0.0)	
Autoimmune thyroiditis	5 (27.8)	12 (66.7)	1 (5.6)	0 (0.0)	< 0.001
Nodular & multi-nodular hyperplasia or goiter	7 (33.3)	13 (61.9)	1 (4.8)	0 (0.0)	
Total	18 (20.0)	36 (40.0)	19 (21.1)	17 (18.9)	

* Calculated by the Chi-square test as the computer memory was not enough to conduct the Fisher's exact test.

Table 4 Rate of thyroid carcinoma by the staining intensity of CK19

	Carcinoma	Benign	Total	p
Staining intensity for CK19	No. (%)	No. (%)	No. (%)	
No staining	0 (0.0)	18 (100.0)	18 (100.0)	
Weak	2 (5.6)	34 (94.4)	36 (100.0)	
Moderate	15 (78.9)	4 (21.1)	19 (100.0)	< 0.001
Strong	17 (100.0)	0 (0.0)	17 (100.0)	
Total	34 (37.8)	56 (62.2)	90 (100.0)	

Higher rates of carcinoma were detected when the staining intensity was moderate (78.9%) or strong (100.0%). None of those

with negative staining had thyroid carcinoma ($P < 0.001$). As shown in Figures 1 and 2.

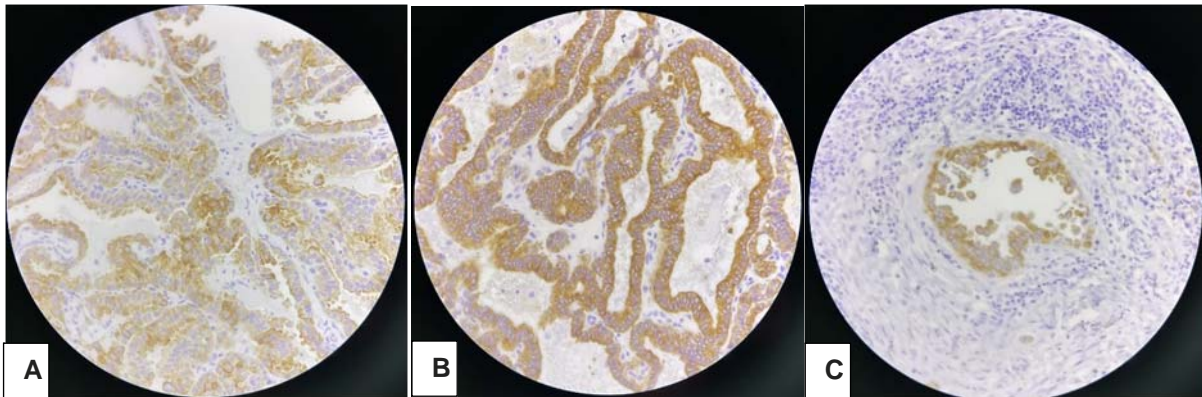


Figure 1 (A) Moderate cytoplasmic and membranous CK19 positivity in cases of PTC (CK19 immunostain original magnification 400x). (B) Strong & diffuse cytoplasmic and membranous CK19 positivity in cases of PTC (CK19 immunostain original magnification 400x). (C) Moderate cytoplasmic and membranous CK19 positivity in cases of lymph node metastasis with PTC (CK19 immunostain original magnification 400x).

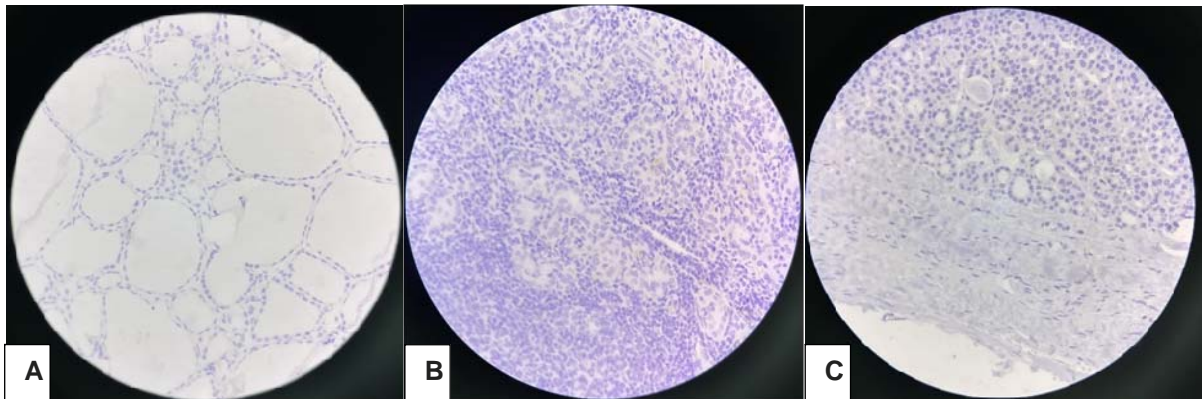


Figure 2 (A) Negative CK19 expression in a case of follicular nodular disease (CK19 immunostain original magnification 400x). (B) Negative CK19 expression in a case of chronic thyroiditis including Hashimoto thyroiditis (CK19 immunostain original magnification 400x). (C) Negative CK19 expression in a case of follicular adenoma (CK19 immunostain original magnification 400x).

Table 4 Selected associations with women's expectations for communication and behaviors with health care providers

Variables	Level of expectation			P-value
	Numerous expectations N (%)	Some expectation N (%)	Few expectations N (%)	
Level of education				
Illiterate	194 (72.4%)	71 (26.5%)	3 (1.1%)	0.028
Read and write	113 (67.3%)	52 (31.0%)	3 (1.8%)	
Primary	344 (70.5%)	138 (28.3%)	6 (1.2%)	
Secondary	92 (66.2%)	42 (30.2%)	5 (3.6%)	
Institute and above	58.6 (78.0%)	55 (41.4%)	0 (0%)	
Occupation				
Husewife	773 (69.6%)	321 (28.9%)	16(1.4%)	0.053*
Employed	35 (59.3%)	23 (39.0%)	1 (1.7%)	
Student	13 (48.1%)	14 (51.9%)	0 (0%)	
Residency				
Urban	446 (68.5%)	199 (30.6%)	6 (0.9%)	0.003*
Suburban	252 (74.1%)	81 (23.8%)	7 (2.1%)	
Rural area	123 (60.0%)	78 (38.0%)	4 (2.0%)	
Parity				
Primipara	143 (60.1%)	95 (39.9%)	0 (0%)	0.001*
Multipara	526 (70.3%)	208 (27.8%)	14 (1.9%)	
Grand multi para	152 (72.4%)	55 (26.2%)	3 (1.4%)	
Satisfied with care				
Yes	746 (79.9%)	185 (19.8%)	3 (0.3%)	<0.001*
No	49 (25.9%)	126 (66.7%)	14 (7.4%)	
Partially	26 (35.6%)	47 (64.4%)	0 (0)	
Satisfied with communication				
Satisfied	642 (91.8%)	57 (8.2%)	0 (0%)	<0.001
Not satisfied	179 (36.0%)	301 (60.6%)	17 (3.4%)	
Duration of last delivery				
1-5 hours	473 (66.9%)	228 (32.2%)	6 (0.8%)	0.010
6-10 hours	238 (71.3%)	90 (26.9%)	6 (1.8%)	
11-15 hours	78 (74.3%)	22 (21.0%)	5 (4.8%)	
16-72 hours	32 (64.0%)	18 (36.0%)	0 (0%)	

*Fisher exact test was used.

Discussion

This study presents women's expectations for health care provider communication and behavior in the labor and delivery room. Two-thirds of the women interviewed had numerous expectations, particularly for emotional and physical support and comfort measures. Women who had numerous expectations were generally satisfied with the care that they received during their most recent delivery and were generally satisfied with the communication of health care providers during their most recent delivery. Having numerous expectations was associated with having a higher level of education, not working outside of the home, living in a suburban area, and having multiple children.

This study's findings align with previous research. For example, in a phenomenological qualitative study in Turkey, researchers analyzed women's expectations of nurses during vaginal birth and found that women wanted physiological support needs in the forms of fulfillment of personal care needs, provision of support to cope with pain, and provision of freedom of mobility; as well as psychological support needs including not being left alone, receiving support from family and friends, having a positive relationship with the birth team, and protection of privacy; and meeting knowledge needs about the process of delivery.¹⁵

An analytical-cross sectional study in Egypt showed that the highest-ranked needs for parturient women during labor were maintaining privacy throughout all procedures, accessibility of nurses, demonstration of empathy, ability to vent and express fear and anxiety, quick response to requests, frequent monitoring, accessibility of caring medical staff, and short delivery.¹⁶ In another cross-sectional study in the same country, mothers were asked about their satisfaction with birth care services. Although most participants were satisfied by the delivery service provided to them, a small group of mothers

were dissatisfied due to lack of communication, perceived lack of privacy during the hospital stay, and obligatory blood donation.¹⁷ In India, research shows that women prioritize the availability of doctors at the facility, availability of medicine, quality of ambulance services, maintenance of cleanliness and hygiene, privacy, patient-provider interaction, and financial cost of care.¹⁸ In Mozambique, a population-based cross-sectional study concluded that satisfaction with childbirth was driven by respect and dignity and emotional support.¹⁹ Finally, research following first-time mothers in Sweden demonstrated that participants felt empowered by trustworthy relationships with professional and their partners. When women felt empowered, they also felt in control, felt the strength of their bodies, and also felt more satisfaction and reassurance, along with experiencing better pain management.²⁰

This study found that having numerous expectations for birth and delivery were associated with having a higher level of education, not working outside of the home, living in a suburban area, and having multiple children. Additional analysis identified a significant association between level of education with work status, residency location, and number of children. This suggests that higher educated women are more likely to, not work outside of the home, live in suburban areas, and have multiple children. Considering that education status is associated with women's empowerment and awareness of one's rights in the sustainable development realm, we suggest that education should be considered a critical factor for improving patient's awareness of their rights.²¹

Because women's satisfaction with verbal and nonverbal communication in the delivery room is associated with their satisfaction with birth care, it is critical to improve the communication skills of health care providers.²²

In this culture and others, patients expect social niceties like greetings, social smiles,

offering a seat, avoiding jargon, adequate time, paraphrasing and empathy. There is also some evidence that patients are increasingly requesting instructions as well as explanations about procedures, and also desire opportunity to express their opinions and fully act in the decision-making process.²³ Additional training for health care providers about these expectations would be beneficial to ensure that providers are meeting patient's needs and expectations.

Post-consultation expectation, perceived health status, and perceived control of health were factors identified as increasing patient satisfaction. In addition, the presence of any disappointments or worries, previous bad experiences with the health care system, and a perceived lack of influence on the consultation had a negative influence on satisfaction.²⁴

Strengths and limitations

This study captures important information that is informative for the development of patient-centered programs and policies. It is worth mentioning that none of the women interviewed had taken an antenatal birth class as these types of classes are not provided in Iraq. As a result, they would not have been educated about standard practices during labor and delivery in an antenatal birth class setting. While the research captured a large sample size, findings from this study are limited by the fact that we used a convenience sample. Further, this study examined women's expectations from midwives, nurses, and physicians as a single unit, rather than examining separate expectations for each type of provider separately, which may be a weakness of the present study.

The decision to ask about expectations for all health care providers as a single unit was made because of the intent to capture a diversity of expectations knowing that, in Iraq, most medical decisions are made by physicians. Given that in Iraq, physicians are the dominant clinical decision makers for patients. One of other limitations of this study is that it focused on public sector, but

did not investigate women's expectations at private sector hospitals and delivery rooms.

Conclusion

This study found that presence, positive and calming verbal and nonverbal expressions, environmental control, encouragement of different positions and mobilization, hygiene, promotion of urinary elimination, and instruction on breathing and relaxation are highly expected by parturient women, followed by demonstrating an effective caring attitude, listening to women's views, application of hot and cold packs, information about routines and procedures, and progress updates. Knowing women's expectations in the delivery room and being able to effectuate them may be one of the best approaches to care planning, and it may also help to increase expecting mothers' satisfaction levels and help them to have a positive birth experience.

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Competing interests

The author declares that she has no competing interests.

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