Diagnostic Accuracy of CK19 in the Diagnosis of Papillary Thyroid Carcinoma

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ABSTRACT

Aim: To determine the diagnostic accuracy of CK 19 expression for the diagnosis of PTC in patients with thyroid nodules, taking histopathology as gold standard.
Study design: Cross sectional survey.
Place and duration of study: Pathology Department of King Edward Medical University & Ganga Ram Hospital Lahore in six months.
Methods: A total of 80 cases of thyroid lesions with suspicion of PTC were included in this study. The immunohistochemical stain CK 19 was performed on the lesions with the suspicion of PTC.Histopathological evaluation of these cases was done for confirmation of PTC or non PTC lesions by the histopathologist. Mean and standard deviation was calculated for quantitative data. Frequency of percentage was calculated for the qualitative data. Sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of CK 19 expression for the diagnosis of PTC, taking histopathology as gold standard.
Results: Out of the 80 casesa histologic diagnosis of papillary thyroid carcinoma was made in 70 cases while 63 cases showed positive staining for CK19. The CK19 showed a sensitivity of 90%, specificity of 80%, positive predictive value of 96.9%, negative predictive value of 53.3% and the diagnostic accuracy of CK 19 was found to be 88.75%.
Conclusion: The results of our present work confirm that CK 19 is a highly sensitive and specific tumour marker.
Keywords: Thyroid lesions, papillary thyroid carcinoma, CK 19.

INTRODUCTION

Thyroid is the most common endocrine gland to undergo neoplastic transformation. Various thyroid lesions may present as diffuse enlargement or palpable solitary nodules. Multinodular goiter is the most common non-neoplastic lesion followed by lymphocytic thyroiditis, benign cyst, Hashimoto's thyroiditis & primary thyroid hyperplasia. Thyroid nodules include benign colloid lesions, adenomas and carcinomas. In Pakistan, Thyroid cancer accounts for 1.5% cases of all malignancies & 92% of all endocrine neoplasms[1,2]. Papillary thyroid carcinoma (PTC) is the most common malignant tumor comprising 70% of thyroid cancers, followed by Follicular carcinoma. The less common tumors are medullary carcinoma, anaplastic and undifferentiated carcinomas[2].

The gold standard for the diagnosis of PTC is histopathology till now and is based on nuclear features. At times, the distinction between papillary thyroid carcinoma (PTC) and non papillary thyroid lesions (non PTC lesions) becomes controversial

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because there are some borderline thyroid lesions with follicular architecture but with questionable nuclear features. Similarly in chronic lymphocytic thyroiditis, the nuclear morphology becomes similar to that of PTC. An interobserver variability for diagnosis also exists. In such controversial conditions, an over or under management of the patient is possible[3,4]. CK 19 is a high molecular weight type 1 intermediate filament protein, member of keratin family. They are responsible for the structural integrity of epithelial cells. Its antibody labels many types of normal and neoplastic epithelia. Previous studies show that it is the most sensitive marker (90.3%) for PTC with a specificity of 83.1% & shows strong diffuse cytoplasmic staining in PTC. CK 19 showed positive expression in 85% cases of PTC and in 26% cases of non PTC. However no such study has been done in our settings. In this study, we shall observe the protein expression & loss by utilizing antibodies to CK19 in PTC[5,6,7]. The rationale of this study is to prove the diagnostic utility of CK19 in papillary thyroid carcinoma which will help in accurate diagnosis of patients thus preventing unusual investigations, follow up and under or over treatment of the patients. This will also help the patients in unnecessary wastage of time and money.

METHODOLOGY

Eighty cases of thyroid nodules with suspicion of PTC and fulfilling the inclusion criteria were included in this study. These cases were referred to us from the surgical departments of Mayo hospital. These surgical thyroid specimens were grossed, fixed in 10% buffered neutral formalin. Sections were processed and stained with hematoxylin and eosin. The immunohistochemical stain CK19 was performed. The pathologist assessed the staining of CK 19 as positive (PTC) or negative (non PTC). Then histopathological evaluation of these cases was done for confirmation of PTC or non PTC lesions. These results along with the patient data including age and sex were recorded on the proforma. The collected information was entered into the SPSS version 10 and was analyzed accordingly. The quantitative variable to be analyzed was age. Mean and standard deviation was calculated for quantitative data. The qualitative variable to be analyzed was gender. Frequency of percentage was calculated for the qualitative data. Sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy of CK 19 expression for the diagnosis of PTC was calculated by generating 2 x 2 tables, taking histopathology as gold standard.

RESULTS

A total of 80 cases were included in the study with mean age of 36.5±10.59 years (Table 1).There were 54(67.5%) patients had age range of 20-40 years and 2 (32.5%) patients had age range of 41-60 years (Table 2). There were 21(26.3%) male patients and 59(73.8%) female patients in this study. In this study, we observed the male-to-female ratio as 1:2.8 (Table 3). CK19 reported 65(81.25%) positive and 15(18.75%) were negative of PTC while histopathology confirmed 70(87.5%) positive and 10(12.5%) negative cases. Thus the sensitivity, specificity, PPV, NPV and diagnostic accuracy of CK19 was calculated as 90%, 80%, 96.9%, 53.3% and 88.75% respectively (Table 4).

Table 1: Descriptive statistics of age (years) of patients

n	80
Mean	36.5
SD	10.59
Minimum	20
Maximum	60
Range	40

Table 2: Distribution of patients in different age groups (years)

Age group	Frequency	%age
20-40 yrs	54	67.5
41-60 yrs	26	32.5

Table 3: Distribution of gender of the patients

Gender	Frequency	%age
Male	21	26.3
Female	59	73.8
Total	80	100

Table 4: Comparison of CK19 Staining vs. Histopathology for diagnosis of positive cases

CK19	Histopathology		Total
	PTC positive	PTC negative	
Yes (positive staining)	63	2	65(81.25%)
No (Negative staining)	7	8	15(18.75%)
Total	70(87.5%)	10(12.5%)	80 (100%)

Sensitivity = 90%,Specificity = 80% ,PPV = 96.9%, NPV = 53.3%,Diagnostic accuracy = 88.75%

DISCUSSION

The thyroid nodules are fairly common and about 20% of the population may present with a dominant nodule in neck or with a diffuse enlargement of neck. Papillary thyroid carcinoma is the most prevalent malignant tumour of thyroid[8]. An increased incidence of this tumour has been noted in the recent years that may be due to the increased use of neck ultrasonography[9]. The greatest trend is seen in young and middle aged women[10]. The most important risk factor is the ionizing radiation. However, some studies suggest that female hormonal and reproductive factors may also be involved[11].

For preoperative diagnosis of the thyroid nodules, FNAC is a well known procedure but there are few limitations to this procedure. It is not a very reliable method to differentiate between benign and malignant follicular tumours and the patients may undergo unnecessary surgical resection[12]. Therefore the treatment and postoperative management of thyroid nodules require an accurate diagnosis[13]. Histopathology is still the gold standard for the diagnosis of thyroid lesions; however, there are some lesions with borderline features that cause problems in the diagnosis[14].

Papillary thyroid carcinoma (PTC) is characterized histologically by distinctive nuclear features i.e., nuclear overlapping, nuclear grooves, clearing and pseudoinclusions. However, these nuclear features may also be seen in Graves' disease (non PTC lesion) showing papillary carcinoma like foci. This may lead to a wrong diagnosis[15]. The initial diagnostic criteria for the diagnosis of papillary thyroid carcinoma was the presence of papillary growth pattern but now the nuclear criteria has also become important rather it has become the diagnostic hallmark of tumour while

the growth pattern is now of less importance. The clear, ground glass, empty or Orphan Annie eyed nuclei can be seen in autoimmune thyroiditis particularly Hashimoto' thyroiditis. Nuclear grooves may be seen in other thyroid lesions including Hashimoto's thyroiditis, adenomatous hyperplasia, diffuse hyperplasia and follicular adenomas particularly hyalinizing trabecular tumour[16]. Similarly, some cases of benign Hurthle cell adenoma (non PTC lesion) may also show a fine chromatin pattern as seen in papillary thyroid carcinoma, this may also lead to a wrong diagnosis[17]. The nodules of Hurthle cell adenoma also show growth pattern similar to the usual papillary thyroid carcinoma. This may also lead to a wrong diagnosis[18].

The problem arises most commonly in the cases of follicular patterned lesions that show questionable nuclear features and incomplete capsular invasion and it becomes difficult to distinguish PTC from benign follicular tumours (non PTC)[14]. Therefore, the follicular variant of papillary thyroid carcinoma is the most controversial entity. The diagnosis of this variant is easy if the nuclear features are characteristic and the growth pattern is non circumscribed and infiltrative.(18)Some lesions of thyroid are rarely completely cystic and the diagnosis becomes difficult[19]. The occult and cystic papillary carcinoma can also lead to a wrong diagnosis. Therefore, the distinction of true papillary carcinoma from the lesions that share some cytologic features with PTC is of clinical importance. Immunohistochemistry can play an important role in the differential diagnosis of these uncertain or borderline cases[20]. CK 19 is the high molecular weight keratin that shows strong and diffuse cytoplasmic staining on H&E slides and helps to differentiate between PTC and non PTC lesions of thyroid. (21)Schroder studied the expression of CK 19 in 1996 over 34 thyroid lesions and reported that all the cases showed strong immunoreactivity for CK 19[22]. Shin observed the expression of CK 19 in 2005 over 115 cases of papillary thyroid carcinoma. Of these, 93(80.9%) cases were positive for CK 19[23].

Nga carried out a study in 2008 over 22 thyroid nodules. In this study 9 cases were diagnosed as papillary thyroid carcinoma and all of them showed diffuse positivity for CK 19[24]. Hussain A.Saleh performed a study in 2009 over 44 thyroid lesions and found that 85% malignant cases are positive for CK 19[12]. A study was performed in China between 2008 and 2011. The results show that 441 cases were diagnosed as PTC and 96.4% of these cases were positive for CK 19. It was noted that the expression of CK 19 was much higher in PTC lesions than in non PTC lesions[25]. Cheung CC, studied 138

cases of papillary thyroid carcinoma and found that 80% cases were positive for CK 19[18].

In the present work, we have studied 80 cases of thyroid lesions with the suspicion of PTC and determined the diagnostic accuracy of CK 19. The sensitivity of CK 19 was found to be 90%, the specificity was 80% and the diagnostic accuracy was 88.75%. These results agreed with results of a study, which reported the sensitivity and specificity of CK 19 were 90.3% and 83.1% respectively. Therefore the results of our current study are comparable with this study and confirm that CK 19 is a very sensitive and specific tumour marker for the diagnosis of PTC[26]. In a study done by Park YJ, the sensitivity and specificity of CK 19 were calculated. The sensitivity was 90.3% and specificity was 83.1%.Therefore the results of our current study are comparable with this study and confirm that CK 19 is a very sensitive and specific tumour marker for the diagnosis of papillary thyroid carcinoma.

CONCLUSION

The results of our present work confirm that CK 19 is a highly sensitive and specific tumour marker. Thus it can play an important role as a positive diagnostic marker in the diagnosis of papillary thyroid carcinoma and may help in the early detection of the tumour. It is recommended that it should be included in the immunohistochemical panel for the diagnosis of papillary thyroid carcinoma.

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