Int J Clin Exp Med 2019;12(2):1929-1935
www.ijcem.com /ISSN:1940-5901/IJCEM0078018

Original Article

Association between the BRAF^{V600E} mutation and ultrasonographic features in papillary thyroid carcinoma: a study of 131 Chinese cases

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Received April 16, 2018; Accepted October 29, 2018; Epub February 15, 2019; Published February 28, 2019

Abstract: To investigate the incidence of BRAF^{V600E} mutation in Chinese patients with papillary thyroid carcinoma (PTC), and analyze the association between BRAF^{V600E} mutation and ultrasonographic (US) features. From October 2015 to December 2017, we retrospectively investigated 131 consecutive Chinese patients with PTC confirmed by postoperative pathology. The incidence of the BRAF^{V600E} mutation was calculated. Univariate and multivariate analysis were performed to evaluate the association between BRAF^{V600E} mutation and US features. A scoring system was created for diagnostic value in predicting BRAF^{V600E} mutation. There were 131 PTCs confirmed by postoperative pathology. The BRAF^{V600E} mutation was observed in 61.8% of PTC (81 of 131). Marked hypoechogenicity (OR: 7.323, P = 0.003), multifocality (OR: 2.911, P = 0.024), microcalcification (OR: 4.244, P = 0.006) and lymph node metastasis (OR: 4.524, P = 0.004) on US were independent predictive factors for the BRAF^{V600E} mutation. The evaluation of all above suspicious US features revealed the specificity and positive predictive value (PPV) were further increased to 100% and 100%, respectively. The BRAF^{V600E} mutation commonly occurrences in Chinese patients with PTC. US features including marked hypoechogenicity, multifocality, microcalcification and lymph node metastasis, can reliably predict the BRAF^{V600E} mutation in PTC. Multiple malignant US features would enhance the specificity and PPV of predicting BRAF^{V600E} mutation in PTC patients.

Keywords: Papillary thyroid carcinoma, BRAF^{V600E} mutation, ultrasonographic features, prediction

Introduction

Papillary thyroid carcinoma (PTC) is the most common subtype of thyroid cancer, which accounts for 85-90% of thyroid carcinoma and its incidence has been increasing during recent years [1, 2]. PTC is an indolent cancer with excellent prognosis with a 10-year survival rate of approximately 95% [3]. However, a subgroup of patients with aggressive features develop recurrence and are associated with adverse prognosis. Several clinical and ultrasonographic (US) characteristics could predict poor prognosis in PTC patients involving older age, large tumor size, solid component, marked hypoechogenicity, multifocality, ill-defined margin, microcalcification, non-parallel shape, and lymph node metastasis.

Ultrasonography is a standard auxiliary examination for patients with thyroid cancer which based on the differences of reflection, absorption and attenuation of US waves in thyroid tissue and surrounding neck tissue [4]. At the beginning, US images were only able to differentiate cystic from solid lesions, but this domain has experienced rapid development, and now includes B-mode imaging, elastography, color Doppler, three-dimensional imaging and US contrast enhancement, allowing radiologists to provide more detailed judgements [5]. Hence, US is more sensitive than palpation and detects thyroid nodules in 19 to 67% of the population without suspected thyroid disease [6].

At the moment, it is believed that the occurrence and deterioration of thyroid disease are associated with genetic level alteration [7]. BRAF mutation is a somatic alteration, which constitutively activates the MAPK signaling pathway [8, 9]. Furthermore, V600E transver-

sion is the main type of BRAF mutation and about 44% of PTC patients were related to V600E mutation [10]. $BRAF^{V600E}$ mutation plays a fundamental role in tumorigenesis and has a closely relationship to the occurrence and deterioration of PTC [11, 12]. However, there are many conflicting reports regarding the association between $BRAF^{V600E}$ mutation and several specific US features of PTC including solid component, marked hypoechogenicity, large tumor size, multifocality, ill-defined margin, microcalcification, non-parallel shape, and lymph node metastasis [13, 14].

In this single-center and retrospective study, we investigated the incidence of $BRAF^{V600E}$ mutation in Chinese patients with PTC, and analyzed the association between $BRAF^{V600E}$ mutation and several US features.

Materials and methods

This retrospective study was approved by the Ethical Committee of the Affiliated Hospital of Jiangsu University, and informed consent was not required for review of patients' images and records. But written informed consent for the evaluation of BRAF was obtained from participant patients prior to cervical surgery.

Patients and thyroid cancer samples

This study was conducted at Affiliated Hospital of Jiangsu University from October 2015 to December 2017. During this period, a total of 188 suspicious thyroid nodules underwent total or near-total thyroidectomy were enrolled in the present study, from which we could obtain histologic pathology and analyze the presence of $BRAF^{V600E}$ mutation. Only nodules that postoperative pathology confirmed PTC were included. Of them, 10 nodules were excluded due to other thyroid carcinomas, including 5 poorly differentiated squamous cell carcinomas, 3 follicular carcinomas and 2 medullary carcinomas. For the remaining 178 nodules, thyroid nodules were included according to the following criterias: (a) US performed < 60 days before cervical surgery. (b) PTC measurement ≥ 10 mm on US. (c) molecular testing for $BRAF^{V600E}$ on pathology specimen. Then, 16 nodules and 24 nodules were excluded due to failing gene detection and size < 1 cm, respectively. Another 7 nodules were excluded because of absence of US images. Finally, 131 PTC were included for further analysis. Clinical information, such as age, gender, hashimoto's thyroiditis (HT) and $BRAF^{V600E}$ mutation, was obtained from medical records.

US and image analysis

Every nodule was studied separately in the conduct. Two experienced radiologists, who were unaware of clinicopathologic characteristics and BRAF results, independently interpreted all US features and recorded the US examination for each PTC. When disagreements appeared, another senior radiologist reviewed the features and made the final decision. We selected the largest tumor as target tumor, when the US features showed multifocality. The following suspicious US features of the target tumor were assessed: tumor size on US, node number, solid component, marked hypoechogenicity, microcalcification, ill-defined margin, non-parallel shape, and lymph node metastasis. Vascularity on US was difficult to evaluate objectively, even using color Doppler technique, so vascularity was not assessed.

BRAF mutation analysis

Genomic DNA was extracted from postoperative paraffin embedded specimens using the QIAamp DNA FFPE Tissue Kit (QIAGEN) following the manufacturer's protocol. For direct DNA sequencing, exon 15, which contains the V600E mutation was amplified by polymerase chain reaction (PCR), followed by the Big Dye terminator cycle sequencing reaction and sequence reading on an ABI PRISM 3730 genetic analyzer (Applied Biosystems, Foster City, CA) [15].

Statistical analysis

Statistical analysis was performed using SPSS for software (ver. 19.0; SPSS Inc. Chicago, IL, USA). The incidence of the $BRAF^{V600E}$ mutation in PTC was calculated. The Student's t-test was used for continuous variables, and Pearson X^2 or Fisher's exact test was used for categorical variables. Sensitivity, specificity, positive predictive values (PPV) and accuracy for predicting BRAF mutation using the index of the number of risk factors were calculated. The area under the receiver operating characteristic (ROC) curve was estimated. Multivariate analysis was used to assess the correlation between these

Table 1. Characteristics of the patients according to the BRAF mutation status

Characteristics	$BRAF^{V600E}$ mutation (N = 131)		*P* value
	Positive	Negative	
Number of patients	81	50	
Age			P = 0.334
Mean ± SD (y)	42.78 ± 10.97	44.78 ± 12.23	
Gender			P = 0.310
Male	15 (18.5%)	13 (26%)	
Female	66 (81.5%)	37 (74%)	
Size on US			P = 0.623
Mean ± SD (mm)	14.30 ± 6.44	13.68 ± 7.81	
Multifocality	34 (42.0%)	10 (20.0%)	P = 0.013
Solid component	80 (98.8%)	48 (96%)	P = 0.558
Marked hypoechogenicity	31 (38.3%)	8 (16.0%)	P = 0.009
Microcalcification	68 (84.0%)	31 (62.0%)	P = 0.008
Ill-defined margin	58 (71.6%)	21 (42%)	P = 0.109
Non-parallel shape	51 (63.0%)	36 (72%)	P = 0.287
Concomitant Hashimoto's thyroiditis	21 (25.9%)	17 (34.0%)	P = 0.323
Lymph node metastasis	30 (37.0%)	6 (12%)	P = 0.002

US: ultrasonographic, PTC: papillary thyroid carcinoma.

predicting factors and $BRAF^{V600E}$ mutation. *P* value ≤ 0.05 was considered to be statistically significant.

Results

Of all 131 cases, 103 (78.6%) were female and 28 (21.4%) were male. Mean ± SD of tumor size and patient age was 14.94 ± 6.13 mm and 43.54 ± 11.47 years, respectively. Solid component was found in 128 PTC (97.7%). 44 (33.6%) cases had multifocal PTC. The marked hypoechogenicity was presented 39 (29.8%) of 131 cases. The number of thyroid nodules with microcalcification was 99 (75.6%) nodules. Ill-defined margin was found in 87 (66.4%) PTCs, and non-parallel shape was present in 44 (33.6%) cases. A total of 38 (29.0%) patients had hashimotos' thyroiditis (HT). The LNM affected 36 (27.5%) of 131 patients. $BRAF^{V600E}$ mutation was observed in 81 (61.8%) patients, revealing a high incidence of $BRAF^{V600E}$ mutation status in the PTC.

Association between $BRAF^{V600E}$ mutation and US features of PTC in univariate analysis

We examined their relationship between $BRAF^{V600E}$ mutation and US characteristics of PTC. As is shown in **Table 1**, marked hypoechogenicity was more likely to present in the BRAF-positive group than the negative group, being 38.3% (31 of 81) in the former vs 16.0% (8 of 50) in the latter (P = 0.009). Microcalcification of PTC was also more common in patients with $BRAF^{V600E}$ mutation than without mutation (P = 0.008). Multifocality was 42.0% (34 of 81) vs 20.0% (10 of 50) in patients with $BRAF^{V600E}$ mutation vs the patients with wild-type (P = 0.013). Lymph node metastasis has a high likelihood of associated $BRAF^{V600E}$ mutation group (P = 0.002). There was a higher trend of larger tumor size in the BRAF mutation group, but this was not statistically significant (P = 0.623). But there was no significant difference in the occurrence rate of BRAF mutation between male and female sex, although there was a trend of higher frequency of BRAF mutations in female patients (P = 0.310). And we did not find a significant difference between patient age and BRAF mutation in this cohort of patients. No significant relationship was also presented with respect to solid component, ill-defined margin and non-parallel (all P > 0.05). Wild-type BRAF displayed a trend of association with hashimoto's thyroiditis (HT) that was not statistically significant (P = 0.323).

Association between $BRAFV^{600E}$ mutation and US characteristics of PTC in multivariate analysis

After evaluating the US features associated with $BRAF^{V600E}$ mutation by chi-squared analysis, we next examined the independent predictive factors for BRAF mutation by multivariate analysis. Marked hypoechogenicity (OR: 7.323, P = 0.003), multifocality (OR: 2.911, P = 0.024), microcalcification (OR: 4.244, P = 0.006) and lymph node metastasis (OR: 4.524, P = 0.004) were risk factors for $BRAF^{V600E}$ mutation in PTC patients (**Table 2**). We found PTC with $BRAF^{V600E}$ mutation was associated with more predictive

Table 2. Multivariate analysis of factors for predicting BRAF mutation in PTC

PTC characteristics	β coefficient	OR	95% confidence interval	*P* value
Marked hypoechogenicity	1.991	7.323	1.958-27.392	0.003
Multifocality	1.068	2.911	1.151-7.360	0.024
Microcalcification	1.446	4.244	1.500-12.004	0.006
Lymph node metastasis	1.509	4.524	1.620-12.633	0.004

PTC: papillary thyroid carcinoma.

Table 3. Association between the number of risk factors and $BRAF^{V600E}$ mutation

	Sensitivity (%)	Specificity (%)	PPV (%)	Accuracy (%)
≥ 1 features	95.1%	18.0%	65.3%	65.6%
≥ 2 features	71.6%	74.0%	81.7%	72.5%
≥ 3 features	29.6%	98.0%	96.0%	55.7%
= 4 features	3.7%	100%	100%	40.5%

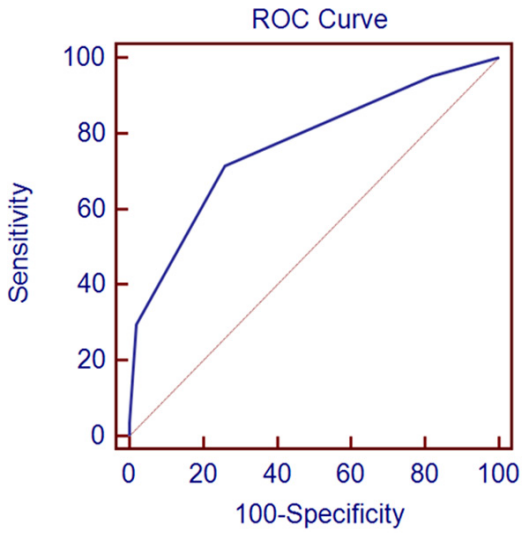

Figure 1. Receiver operating characteristic (ROC) curve of the association between the number of predictive factors and $BRAF^{V600E}$ mutation in PTC. PTC: papillary thyroid carcinoma.

factors than without mutation, and as the number of factors increased, the specificity and PPV also significantly increased. The collective evaluation of all four risk factors revealed that specificity and PPV were further increased to 100% and 100%, respectively (**Table 3**). A ROC curve was created to verify the association between the number of predictive factors and $BRAF^{V600E}$ mutation (**Figure 1**). The area under the curve was 0.767 (P = 0.000), demonstrating that the test was accurate.

Discussion

Inconsistent results regarding the association between $BRAF^{V600E}$ mutation and US features of PTC prompted us to investigate their relationship. In this investigation, a frequency of 61.8% for BRAF mutation in Chinese PTC patients found seemed to be higher than previously reported [16]. One explanation is that relatively high iodine intake may cause the observed occurrence of $BRAF^{V600E}$ mutation [17]. Our study is conducted in southeastern area in China, where people consume high dietary iodine from rich sea food [18]. However, the prevalence of the $BRAF^{V600E}$ mutation is not high in Japan, in which the population also intakes high dietary iodine [19]. Hence, large-scale studies will be necessary to determine the relationship between the prevalence of the $BRAF^{V600E}$ mutation in PTC and iodine intake in the Chinese patients.

Xing et al. presented a strong association of BRAF-positive status with aggressive US features and poor prognosis [13]. A similar study was also reported in the finding of Lin et al. [20]. In contrast, Li et al. showed a negative association between $BRAF^{V600E}$ status and several US features [14]. Although different tumor size, clinical data collection, and methods used to detect $BRAF^{V600E}$ mutation might be taken into account, there is no clear explanation for these ambiguous results.

According to previous studies, US features of malignant thyroid nodules are well presented including solitary, marked hypoechogenicity, ill-defined margin, multifocality, microcalcifications, non-parallel shape and lymph node metastasis [21, 22]. The study by Lee et al. found that the correlation of $BRAF^{V600E}$ status with malignant US characteristics, these results were very likely confounded by the small mean size (< 1 cm) of the studied PTC [23]. In the present study, we examined a series of PTC ≥ 10 mm to investigate the relationship between BRAF mutation and several US features.

As our knowledge, many previous studies analyzed the relationship between hypoechogenicity and $BRAF^{V600E}$ mutation, and only a handful investigation has reported the associated of

marked hypoechogenicity with $BRAF^{V600E}$ mutation. Marked hypoechogenicity was defined as the echogenicity was lower than the adjacent strap muscle, and we found marked hypoechogenicity was an independent risk factor for $BRAF^{V600E}$ mutation. Multifocality is traditionally considered indication for increased risk of aggressiveness and tumor recurrence, and multifocality indicated more aggressive than unifocal tumor. In our study, there was a strong relationship between the genetic mutation and multifocality, which is consistent with previous findings [24]. Zhang et al. [25] revealed that microcalcification was related to BRAF mutation, which is similar to our findings. In regard to the relationship between the BRAF mutation and LNM. One meta-analysis including 5655 PTC patients, revealed a significant relationship between the BRAF mutation and LNM, extrathyroidal extension (ETE), advanced tumor stage (T3/T4) and recurrence [26]. Liu et al. also suggested a significant relationship between BRAF mutation and lymph node metastasis [27]. Our results also showed a positive relationship between BRAF positivity and LNM. There have been a few studies on the effects of coexisting HT with PTC on the BRAF status. Loh et al. reported that patients with PTC concomitant HT had a good prognosis, because the low frequency of extrathyroid extension (ETE), lymph nodal metastasis and distant metastasis [28]. Interestingly, our results demonstrated the incidence of BRAF-positive status was less frequent in PTC patients concomitant HT than not concomitant HT (25.9% vs 34.0%), even though the discrepancy has no statistical significance. It is similar to that in a Korean cohort with PTC reported by Kim et al. [29].

Similar to the previous study [5], we found that PTC with $BRAF^{V600E}$ mutation was associated with more suspicious features than without mutation, multiple risk factors could enhance the specificity and PPV of predicting BRAF mutation. Therefore, our present study, together with other previous studies, strongly established that $BRAF^{V600E}$ mutation plays an important role in the aggressiveness of PTC and thus represents potential prognostic molecular marker that may be useful in evaluating risk stratification of PTC patients.

The study existed following limitations. The study existed following limitations. Firstly, the size of our study was relatively modest. Secondly, our study was a retrospective observational study, so selection bias is inevitable. Thirdly, we did not evaluate the Eastographic or Doppler of PTC features, which could provide more detailed diagnostic information. Thus, prospective, large-scale studies with Doppler or Elastographic evaluations are necessary to be carried out.

In summary, we presented a study of 131 PTC nodules to demonstrate the mutation-$BRAF^{V600E}$ mutation commonly occurrences in Chinese patients with PTC. Ultrasonographic features including marked hypoechogenicity, multifocality, microcalcification and lymph node metastasis, can reliably predict the $BRAF^{V600E}$ mutation in PTC. Multiple risk factors would enhance the specificity and PPV of predicting $BRAF^{V600E}$ mutation in Chinese patients with PTC.

Acknowledgements

Supported by Maternal and Child Health Research Project of Jiangsu Province (F201822), Zhenjiang Social Development Foundation Programme (SH2015074) and the 17th batch of students' research projects of Jiangsu University (17A062).

Disclosure of conflict of interest

None.

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