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Original Article

Metastasis and ultrasound profiles in classical and follicular variant papillary thyroid carcinoma

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Abstract

Background : Papillary thyroid carcinoma (PTC) is the most common carcinoma, accounting for more than 90% of all malignancies where the most common variants are classical papillary thyroid carcinoma (classical PTC) and follicular variant papillary thyroid carcinoma (PTCVF). The characteristics of previous thyroid disease history, regional metastases, and ultrasound examination which may influence differentiation between classical PTC and PTCVF has not been published. The aim of this study was to describe the differences in the history of previous thyroid disease, metastases, and ultrasound examination abnormalities between classical PTC and PTCV Fat Dr. Kariadi Hospital, Semarang.
Methods : A cross sectional study from January to June 2019 in Dr. Kariadi Hospital Semarang using consecutive sampling method obtained 18 medical records of patients with classical PTC cases and 20 medical records with PTCVF cases. The independent variables were history of previous thyroid disease, regional metastases, and ultrasound examination abnormalities, all of which were on an ordinal scale, were analyzed using non-parametric Fisher's Exact test and Mann Whitney test.
Results : History of previous thyroid disease, regional metastases, ultrasound size abnormalities and abnormalities ultrasound nodal were not different in both group (p = 0.474, 0.174, 0.567, and 0.595 respectively).
Conclusion : There were no differences in the history of previous thyroid disease, regional metastases, and ultrasound examination abnormalities between classical PTC and PTCVF patients at Dr. Kariadi Hospital, Semarang.

Keywords : Classical papillary carcinoma of the thyroid; follicular variant papillary thyroid carcinoma; thyroid disease

INTRODUCTION

A new case of a patient with a PTC at Dr. Kariadi Hospital, Semarang is quite high. The most variants are classical PTC and PTCVF which have not been frequently reported among new PTC in Indonesia. Diagnosing PTC using histopathological examination as gold standard, is somewhat subjective. The criteria for benign or malignant are only based on the description of the papillary nuclear features and microscopic architecture.[1,2] Therefore, itis important to correspond with clinical characteristics of the patient to obtain accurate diagnosis. This clinical examination is not widely studied and published, especially in Dr. Kariadi Hospital, Semarang.

The hypothesis of this study was there were differences in the characteristics of previous thyroid disease history, metastases, and ultrasound examination results between classical PTC and PTCVF in total thyroidectomy patients at Dr. Kariadi Hospital, Semarang. The purpose of this study was to determine the differences of previous thyroid disease history, metastases, and ultrasound examination results between classical PTC and PTCVF in total thyroidectomy patients at Dr. Kariadi Hospital, Semarang.

METHODS

This research has received permission from the Ethics Commission for Health Research, Faculty of Medicine, Diponegoro University. Permit was granted on June 4, 2020 with number No. 98 / EC / KEPK / FK-UNDIP / VIP / 2020.

This study was an observational study design with a cross sectional method. Based on the cross sectional formula, the minimum required sample size was 30 samples. Data used were secondary data from medical records available in Dr. Kariadi Hospital, Semarang from January to June 2019.

The subjects of this study were patients who had been diagnosed as classical PTC and PTCVF in Dr. Kariadi Hospital, Semarang who met inclusion criteria. Sampling method used was consecutive sampling. The inclusion criteria in this study were patients who were diagnosed as patients with classical PTC or PTCVF based on histopathological examination and data from medical records including: patient identity, contact person, history of previous thyroid disease, stage, metastases, and ultrasound examination results.

Variables in this study included the characteristics of previous thyroid disease, regional metastases, and ultrasound examination abnormalities where these variables were an ordinal scale.

Management of medical record data includes editing, coding, and analysis using SPSS (Statistical Package for the Social Sciences) program. The ordinal and nominal data scale are presented in the form of frequency and proportion.

To obtain the different between variables, data

TABLE 1
Clinicopathological characteristics of patients with classical PTC and PTCVF

Parameter	Classical PTC	PTCVF	Total
History of previous thyroid diseases			
- Previous disease (+)	1 (5.6%)	0 (0%)	1 (2.6%)
- Previous disease (-)	17 (94.4%)	20 (100%)	37 (97.4%)
Regional metastasis			
- Metastasis (-)	12 (66.7%)	17 (85%)	29 (76.3%)
- 1 lymph node metastasis	1 (5.6%)	1 (5%)	2 (5.3%)
- Metastasis > 1 lymph node	5 (27.8%)	2 (10%)	7 (18.4%)
Ultrasound abnormalities			
- T1, T1A, T1b	8 (44.4%)	5 (25%)	13 (34.2%)
- T2	3 (16.7%)	7 (35%)	10 (26.3%)
- T3	6 (33.3%)	8 (40%)	14 (36.8%)
- T4	1 (5.6%)	0 (0%)	1 (2.6%)
- Lymph node magnification (-)	2 (11.1%)	1 (5%)	3 (7.9%)
- Level 6 lymph node magnification	0 (0%)	0 (0%)	0 (0%)
- Level 1-5 lymph node magnification	16 (88.9%)	19 (95%)	35 (92.1%)

with ordinal and nominal scales were tested using Mann Whitney test and Fisher's Exact test with the degree of significance used was $p<0.05$.

RESULTS

The study was conducted for approximately 3 weeks between June – July 2020. A total of 33 medical records of classical PTC patients were obtained, with 18 cases met the inclusion criteria. As for PTCVF patients a total of 51 medical records were obtained with 20 cases matched the inclusion criteria. The clinicopathological data of patients are presented in table 1.

This study showed that all PTCVF patients had no previous history of thyroid disease, where as in classical PTC only one patients had a history of previous thyroid disease.

Based on histopathology data, most patients had no regional metastasis and small number of them presented metastasis at 1 lymph node or more. This trend applied in both groups.

Based on ultrasound data for primary nodule size (T), the proportion of subjects in both groups were spread similarly in the category of T1 to T4. In addition to the size of primary nodules, an equal number of regional lymph node nodules (N) metastasis were observed in both groups.

Differences in clinicopathological variables between Classical PTC and PTCVF

Previous history of thyroid disease, regional metastases, and ultrasound abnormalities were data on an ordinal scale, so the data were analyzed using the Chi Square test and the fisher's exact test to look for significant differences where the p value was <0.05.

Based on Mann Whitney test and Fisher's Exact test, previous thyroid disease history, regional metastases, ultrasound size abnormalities and ultrasound nodal abnormalities were not different in patients with classical PTC and PTCVF.

DISCUSSION

Historical differences in previous thyroid disease between Classical PTC and PTCF variables

Based on this study, it was only one patient with classical PTC in Dr. Kariadi Hospital, Semarang had a history of previous PTC disease. Meanwhile, all PTCVF cases in

TABLE 2
Differences of clinicopathological variables using Classical PTC and PTCVF

	Classical PTC	PTCVF	*p*
1. Mann Whitney test			
a. Regional metastasis			0.174
- Metastasis (-)	12 (66.7%)	17 (85%)	
- 1 lymph node metastasis	1 (5.6%)	1 (5%)	
- Metastasis >1 lymph node	5 (27.8%)	2 (10%)	
b. Ultrasound size abnormalities			0.567
- T1, T1A, T1b	8 (44.4%)	5 (25%)	
- T2	3 (16.7%)	7 (35%)	
- T3	6 (33.3%)	8 (40%)	
- T4	1 (5.6%)	0 (0%)	
2. Fisher's Exact test			
a. History of previous thyroid disease			0.474
- Previous disease (+)	1 (5.6%)	0 (0%)	
- Previous disease (-)	17 (94.4%)	20 (100%)	
b. Ultrasound node abnormalities			0.595
- Lymph node magnification (-)	2 (11.1%)	1 (5%)	
- Level 6 lymph node magnification	0 (0%)	0 (0%)	
- Level 1-5 lymph node magnification	16 (88.9%)	19 (95%)	

Dr. Kariadi Hospital, Semarang had no history of previous thyroid disease. This could be due to the dominant point mutation in the classical PTC, namely $BRAF_{V600E}$, which is related to aggressiveness through RAF kinase activity.[3–5] Previous research conducted in the United States stated that the probability of having recurrent disease was significantly higher for patients with classical PTC than for PTCVF.[6]

There were no significant difference of previous history of thyroid disease between classical PTC and PTCVF in Dr. Kariadi Hospital, Semarang. This result was in contrary with the results found in a study in the United States and South Korea. It is probably due to the lack of variation in data when compared to the previous studies which had 542 samples in the United States study and 249 samples in South Korea study.[6,7,11]

Regional metastatic differences between classical PTC and PTCVF

The incidence of regional lymph node metastases were more common in classical PTC patients accounting for 6 cases. Meanwhile, in PTCVF, there were 3 cases of regional lymph node metastases. It may be explained that the $BRAF_{V600E}$ gene mutation occurs in classical PTC can increase RAF kinase activity. A high RAF kinase activity will lead to invasion (uncontrolled cleavage), metastasis, and proliferation. It is different from PTCVF which mutation of $BRAF_{K601E}$ gene increases RAF kinase activity not as high as $BRAF_{V600E}$.[8,9,10] This is consistent with research conducted in South Korea where the incidence of regional metastasis is more common in classical PTC compared to PTCVF accounting for 36.7% of classical PTCs that have experienced regional metastases and 9.6% of PTCVF who experienced regional metastases.[11] Similar to a study conducted in the United States, regional metastases were more prevalent in classical PTC (47.8%) than in PTCVF (27.3%).[6]

Differences in ultrasonographic examination abnormalities between Classical PTC and PTCVF

The first aspect of ultrasound examination abnormalities showed the smallest primary nodule size (T1) was more common in classical PTC than in PTCVF. Likewise, the size of the largest primary nodule (T4) which includes extrathyroid spreading is more common in classical PTC than PTCVF, counted only 5.6% in classical PTC while no sample in PTCVF observed with T4 size. Meanwhile, the T2 nodule size was more frequent in PTCVF (35%) compared to classical PTC (16.7%), similar with T3 size which was more common in PTCVF (40%) than in classical PTC (33.3%). This is consistent with research in the United States for proportion of T1 on classical PTC (44.33%) more than PTCVF (40.5%), T2 on PTCVF (32.9%) more than classical PTC (25%), T3on PTCVF (13%) more than classical PTC (7.4%), and T4 on classical PTC (23.2%) more than PTCVF (13.6%). In that study it was also stated that PTCVF had a larger primary nodule size but was limited to the thyroid (T3), in contrast to classical PTC which had a high risk of spreading to the extra thyroid tissue (T4). It may be conclude that classical PTC is unique and more aggressive biologic tumor with more metastatic potential than PTCVF. This interpretation is supported by the TCGA analysis, which reveals that classical PTC and PTCVF differ based on the principle of somatic mutation and cellular signaling, which leads to aggressive behavior in the classical PTC phenotype.[6,12,13]

In the second aspect, an ultrasound nodal abnormality assessment which was performed in this study, showed that negative (N0) enlargement of lymph nodewere more frequent in classical PTC than PTCVF. While lymph node enlargement level 1-5 (N1b) were more often found in PTCVF, there were no cases of both classical PTC and PTCVF with enlargement of lymph node level 6 (N1a). Based on previous research conducted in United States, negative lymph enlargement occurs more frequently in classical PTC than PTCVF. This result was consistent with our study. However, the enlargement of lymph node level 6 and level 1-5 in the previous study stated that it was more common in classical PTC than PTCVF.[6]

The abnormalities between regional metastases based on biopsy, pathology, anatomy and ultrasonography in this study showed that on biopsy examination there was a higher lymph node metastasis found in classical PTC than PTCVF, which was in line with the results of previous studies, where as USG examination showed higher proportion in PTCVF group. This proved that ultrasound examination alone was not enough to diagnose classical PTC and PTCVF because ultrasound examination can only detect enlarged lymph node without assessing malignancy, in contrast to the pathological anatomical biopsy examination which is the gold standard examination to support the diagnosis of classical PTC and PTCVF.[6,14,15]

CONCLUSION

It can be concluded that there were no differences in the history of previous thyroid disease, regional metastases, and ultrasound examination abnormalities between classical PTC and PTCVF patients in Dr. Kariadi Hospital, Semarang. Further research is needed to determine other clinical aspects that can distinguish classical PTC and PTCVF, and direct intervention is needed for patients with classical PTC and PTCVF to find environmental factors regarding radiation exposure.

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