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Ultrasonographic Characteristics Analysis of Papillary Thyroid Carcinoma with Hashimoto's Thyroiditis in Different Functional States

Yafei Guo[1,a], Wenjing Yang[2,b], Yuhang Tan[1,c], Qili Zhang[1,d], Ruijun Guo[1,e,*]

[1]Department of Ultrasound, Beijing Chaoyang Hospital of Capital Medical University, Beijing, China
[2]Department of Thyroid and Neck Surgery, Beijing Chaoyang Hospital of Capital Medical University, Beijing, China
[a]18332756922@163.com, [b]Alice1998@gmail.com, [c]875711025@qq.com, [d]18862186940@163.com, [e]ruijunguo@126.com
**Corresponding author*

Abstract: *The ultrasonographic characteristics of thyroid papillary carcinoma with and without hashimoto's thyroiditis were compared and analyzed to explore the effect of hashimoto's thyroiditis on ultrasonographic characteristics of thyroid papillary carcinoma, in order to improve the accuracy of ultrasonic diagnosis. Method 91 patients with thyroid papillary carcinoma confirmed by surgical resection and pathological biopsy in Beijing Chaoyang Hospital, Capital Medical University from September 2018 to November 2021 were retrospectively analyzed. Result The maximum diameter, blood flow grade and lymph node metastasis rate of papillary thyroid carcinoma in hashimoto's thyroiditis group were significantly higher than those in non-hashimoto thyroiditis group (P < 0.05). There were significant differences in the growth pattern, hardness and Ratio of papillary thyroid carcinoma among the three subgroups (P < 0.05). Conclusion Under different functional states, thyroid papillary carcinoma combined with hashimoto's thyroiditis showed differences in the growth pattern, hardness, blood grade and other sonographic characteristics.*

Keywords: *Hashimoto's thyroiditis; Papillary thyroid carcinoma; Shear wave elastography; Superb Micro-Vascular Imaging; Ultrasonography*

1. Introduction

Hashimoto's thyroiditis (HT) is the most common autoimmune thyroid disease, also known as chronic lymphocytic or autoimmune thyroiditis[1,2]. In recent years, the incidence of HT has increased rapidly, especially in young and middle-aged women.HT can destroy thyroid tissue through cellular and antibody mediated immune processes and its main pathological features are lymphocytic infiltration, formation of lymphatic follicles, interstitial fibrosis, and destruction of normal thyroid tissue[2].Laboratory tests of this disease are characterized by elevated thyroid peroxidase antibody(TPOAb) and thyroglobulin antibody(TGAb).With the progression of the disease, thyroid function can be roughly divided into three stages: normal, hyperactive and hypothyroidism. At first, thyroid function is usually normal or even hyperactive, but eventually it inevitably develops into hypothyroidism[3,4].The diagnosis of HT requires a combination of clinical features, serum anti-thyroid antigen antibodies and sonographic findings.

Papillary thyroid carcinoma(PTC) accounts for 70% ~ 80% of all thyroid cancers, and it is the most common thyroid malignant tumor at present, among which the papillary thyroid microcarcinoma(PTMC) is less than 1cm in diameter. The incidence of PTC with HT has been increasing year by year[5]. Although the exact relationship between them is not clear at present, some studies have found that patients with HT have a higher risk of PTC[6,7].Ultrasonography is the preferred imaging method for PTC, which findings are typical usually. However, when patients concomitant with HT, the ultrasound findings are sometimes atypical ,which are related to thyroid function status.

In this study, the ultrasonographic characteristics of thyroid papillary carcinoma with and without hashimoto's thyroiditis were compared and analyzed to explore the effect of hashimoto's thyroiditis on ultrasonographic characteristics of thyroid papillary carcinoma, in order to further improve the diagnostic accuracy of PTC with HT.

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2. Materials and methods

2.1. Patients

A retrospective study was performed on patients with PTC confirmed by surgical resection and pathological biopsy in Beijing Chaoyang Hospital, Capital Medical University from September 2018 to November 2021. The inclusion criteria were as follows: patients who have complete pathological data, laboratory examination, conventional ultrasound, shear wave elastography and superb micro-vascular imaging data. The exclusion criteria were as follows: patients who didn't have complete datas and patients who suffered from other types of thyroid malignancies, other autoimmune diseases and other thyroid dysfunction. This study was retrospective and did not involve patients' privacy, so informed consent was not required.

2.2. Study design

According to pathological results and laboratory examination, eligible subjects were divided into Hashimoto's group(HT group) and non-Hashimoto's group(NHT group).HT group was further divided into three different subgroups according to the levels of thyroid-stimulating hormone(TSH) and free thyroxine(FT3 and FT4):normal thyroid function group(normal group), hyperactive thyroid function group(hyperactive group) and hypoactive thyroid function group(hypoactive group).Record and analyse the age and sex of the patients, the size, growth pattern, boundary, acoustic halo, internal echo, calcification, blood flow, lymph node metastasis, Young's modulus, Ratio value and other ultrasonic parameters of thyroid papillary carcinoma nodules.

2.3. Ultrasonography examination

All included patients underwent an ultrasound examination before surgery. The ultrasound examination was performed using Aplio500 ultrasound system with a 5-10MHz linear array probe. Each patient was placed in the supine position while lying on the examination bed and the neck was fully extended. The size, boundary, internal structure, internal echo, calcification and status of the lymph nodes was observed and recorded. All of the nodules were separately evaluated by superb micro-vascular imaging(SMI) and color Doppler flow imaging(CDFI)with Adler grade, vascular morphology and peripheral blood flow[8].

After B-mode US, SWE scans of suspicious malignant nodules were performed using linear-array transducer. The operator placed the probe gently on patients neck and avoided compress to minimize the probes impact on elasticity parameters. Setting the size of the sampling frame was 2-3 times of the lesion, placing the lesion in the center of the sampling frame and setting the detection range was 0-200 KPa. The patient was asked to hold breath, and the image was frozen after the shear wave curve met the quality control requirements. After optimal SWE images were obtained, four 2-mm diameter circular region-of-interest (ROI) was placed in the thyroid nodule , while the other ROI was placed on the normal thyroid parenchyma. The SWE system automatically calculated elasticity parameters. Young's modulus is the mean value of the four ROI and Ratio is the ratio of the mean stiffness of the thyroid nodule to that of the normal thyroid parenchyma **(Figure 1).**

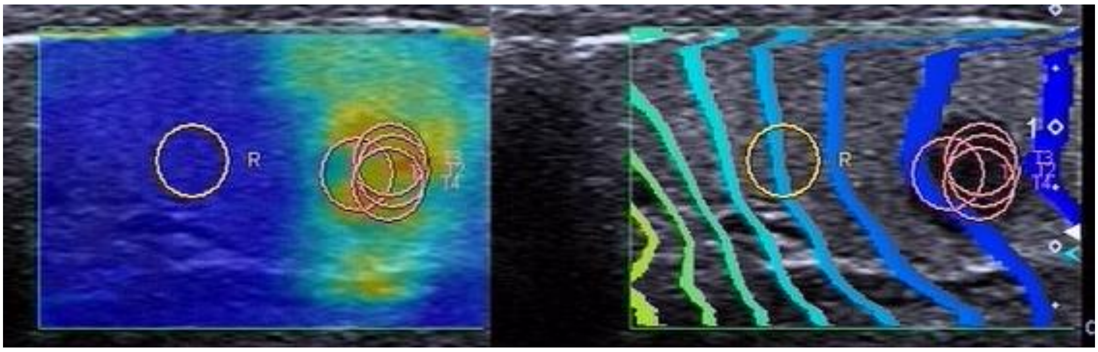

Figure 1: Method of SWE measuring Young's modulus and Ratio

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2.4. Statistical analysis

The statistical analysis was performed using SPSS 21.0 (SPSS Inc., Chicago, IL, USA). The continuous quantitative data are shown as the mean ± standard deviation. An independent two-sample Student's t-test was conducted to compare the data displaying a normal distribution. The categorical variables are shown as percentages, and a chi-square analysis or Fisher's exact test was applied to compare the results. P-value < 0.05 indicated a significant difference.

3. Results

91 patients were included in this study, with 119 nodules, and 52 patients in the HT group, 39 patients in the NHT group. There were 12 men and 79 women with an average age of 44.37 ±11.46 years and a range of 24 to 70 years. There were no significant differences in age and gender between two groups ($P > 0.05$).

3.1. Ultrasonographic characteristics of nodules between HT group and NHT group

Table 1: Ultrasonographic characteristics of nodules between HT group and NHT group

Demographic and ultrasonographic characteristics	HT group（*n*=58）	NHT group（*n*=61）	t/χ^2	*P* value
Age	43.35±10.53	46.03±12.58	0.084	0.271
Sex				
male	6	6	0.288	0.592
female	46	33		
The largest diameter of the nodule	0.85±0.47cm	0.68±0.36cm	2.236	0.027*
Growth pattern				
vertically	39/58(67.2%)	43/61（70.5%）	0.147	0.702
horizontally	19/58(32.8%)	18/61（29.5%）		
Margin				
regular	6/58（10.3%）	12/61（19.7%）	2.015	0.156
irregular	52/58（89.7%）	49/61（80.3%）		
Echogenicity				
hyperechogenicity	5/58（8.6%）	9/61（14.8%）	5.413	0.067
hypoechogenicity	52/58（89.7%）	46/61（75.4%）		
marked hypoechogenicity	1/58（1.7%）	6/61（9.8%）		
Echo halo				
yes	6/58（10.3%）	6/61（9.8%）	0.008	0.972
no	52/58（89.7%）	55/61（90.2%）		
Calcification				
no	30/58（51.7%）	28/61（45.9%）	0.603	0.704
microcalcification	18/58（31.0%）	23/61（37.7%）		
non-microcalcification	10/58（17.3%）	10/61（16.4%）		
SMI				
0	8/58（13.8%）	21/61（34.4%）	8.170	0.043*
I	12/58（20.75%）	12/61（19.7%）		
II	20/58（34.5%）	14/61（22.9%）		
III	18/58（31.0%）	14/61（22.9%）		
Lymph node metastasis				
Yes	32/58（55.2%）	19/61（31.1%）	7.007	0.008*
no	26/58（44.8%）	42/61（68.9%）		
Young's modulus	57.51±25.74Kpa	53.15±28.31Kpa	0.877	0.382
Ratio	2.58±1.01	2.73±1.33	0.679	0.498

*Statistically significant difference

There were no significant differences in growth pattern, boundary, internal echo, acoustic halo, calcification, Young's modulus and Ratio of papillary thyroid carcinoma nodules in HT group and NHT group ($P > 0.05$).Compared with NHT group, papillary thyroid carcinoma nodules in HT group had larger diameter and higher lymph node metastasis rate ($P < 0.05$).There was also a significant difference in Adler flow grade between the two groups ($P < 0.05$). The majority of tumor nodules were grade II and III in the HT group, while grade 0 and I in the NHT group **(Table 1).**

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3.2. Ultrasonographic characteristics of nodules between three subgroups

Table 2: Ultrasonographic characteristics of nodules among three subgroups

Demographic and ultrasonographic characteristics	normal group (*n*=22)	hyperactive group (*n*=19)	hypoactive group (*n*=17)	$t/F/\chi^2$	*P* value
Age	44.24±11.03	45.67±11.49	40.00±8.56	1.260	0.293
Sex					
male	1	3	2	2.068	0.350
female	20	12	14		
The largest diameter of the nodule	0.93±0.43cm	0.89±0.65cm	0.71±0.20cm	1.076	0.348
Growth pattern					
vertically	17/22（77.32%）	15/19（78.9%）	7/17（41.2%）	7.430	0.028*
horizontally	5/22（22.7%）	4/19（21.1%）	10/17（58.8%）		
Margin					
regular	1/22（4.5%）	2/19（10.5%）	3/17（17.6%）	1.814	0.419
irregular	21/22（95.5%）	17/19（89.5%）	14/17（82.4%）		
Echogenicity					
hyperechogenicity	2/22（9.15%）	1/19（5.3%）	2/17（11.8%）	2.171	0.945
hypoechogenicity	19/22（86.4%）	18/19（94.7%）	15/17（88.2%）		
marked hypoechogenicity	1/22（4.5%）	0/19（0）	0（0）		
Echo halo					
yes	2/22（9.1%）	1/19（5.3%）	1/17（5.9%）	0.265	1.000
no	20/22（90.9%）	18/19（94.7%）	16/17（94.1%）		
Calcification					
no	10/22（45.5%）	11/19（57.9%）	9/17（52.9%）	1.263	0.881
microcalcification	7/22（31.8%）	5/19（26.3%）	6/17（35.3%）		
Non-microcalcification	5/22（22.7%）	3/19（15.8%）	2/17（11.8%）		
SMI					
0	4/22（18.2%）	1/19（5.3%）	3/17（17.6%）	7.257	0.357
I	9/22（40.9%）	4/19（21.1%）	5/17（29.4%）		
II	5/22（22.7%）	9/19（47.4%）	7/17（41.2%）		
III	4/22（18.25）	5/19（26.2%）	2/17（11.8%）		
Lymph node metastasis					
yes	14/22（63.7%）	11/19（57.9%）	7/17（41.2%）	2.043	0.428
no	8/22（36.3%）	8/19（42.1%）	10/17（58.8%）		
Young's modulus（Kpa）	45.28±11.32Kpa	55.43±23.91Kpa	75.66±31.43Kpa	8.571	0.001*
Ratio	2.38±0.80	3.33±0.87	2.00±0.96	11.396	0.001*

*Statistically significant difference

There were no significant differences in the maximum diameter, boundary, internal echo, halo, calcification, blood flow and lymph node metastasis of nodules in three subgroups ($P > 0.05$).However, there were significant differences in growth pattern, Young's modulus and Ratio value ($P < 0.05$).Compared with normal subgroup and hyperactive subgroup, nodules in the hypoactive subgroup tended to grow horizontally, rather than vertically. The Young's modulus of nodules in three subgroups increased successively, and the difference was statistically significant ($P < 0.05$). The Ratio of nodules in hyperactive subgroup was the highest, while that in hypoactive subgroup was the lowest ***(Table 2)***.

4. Discussion

HT is the most common autoimmune thyroid disease, which tends to occur in women between 30 and 50 years old. PTC is the most common thyroid malignant tumor at present, which accounts for 70% ~ 80% of all thyroid cancers. In recent years, the incidence of PTC with HT is increasing[1,2,3]. An epidemiological study reported that PTC co-existed with PTC on average about 23%[9], and in this study, this value was higher. The exact relationship between them has not been elucidated, but some studies have suggested that they have same immune link and same gene expression, and patients with HT have a higher risk of PTC[6,7,10,11].Ultrasonography is one of the most important methods to diagnose thyroid diseases at present, including conventional two-dimensional ultrasound, Doppler ultrasound, shear wave elastography, superb micro-vascular imaging and contrast-enhanced ultrasound.

PTC usually have typical appearances on ultrasonography, however, when combined with HT, the lesion may lack typical ultrasound appearances due to changes in the background echo and the changes in blood flow ,which increased the difficulty of identification[12].

In this study, there were no significant differences in growth pattern, boundary, internal echo, acoustic halo, calcification, Young's modulus and Ratio value of nodules between PTC with and without HT. The maximum diameter of PTC nodules with HT was larger than that without HT, and the lymph node metastasis rate was higher. But a recent meta-analysis found that patients with PTC and HT at same time had a lower rate of lymph node metastasis, lower malignancy, and better prognosis[13].This is different from the results of this study, which may be due to the small sample size and other confounding factors have not been excluded. In addition, we found that the nodules in the hypothyroidism group tended to grow horizontally rather than vertically as is typical.

SMI is a new type of blood flow visualization technology that can more sensitively display low-speed, microscopic blood vessels inside lesions that CDFI cannot[14].The blood supply inside the lesion is related to the histological structure of the lesion, the more fibrous tissue, the less blood flow, and the more tumor cells, the more blood flow[15].In this study, we found that the blood of PTC nodules with HT were dominated by grade II and III , while dominated by grade 0 and I in nodules without HT. However, there was no significant difference in blood grade of lesions at the three stages of thyroid function. In HT patients, the thyroid tissue was attacked and damaged, resulting in changes in the levels of TH and TSH in the blood. TSH can stimulate thyroid follicular epithelial cell proliferation by stimulating TSH receptor, producing vascular endothelial growth factor, and then stimulating endothelial cell regeneration and blood vessel formation.TH itself can directly affect the synthesis of blood vessels, and can also promote vasodilation by regulating PKG/VASP signaling pathway of vascular smooth muscle cells[16-17]. Therefore, the blood supply of thyroid gland in HT changes, which further affects the blood supply of cancer nodules. There is no difference in blood signals in cancer nodules under different functional states, which may be related to the changes of histological structure and hormone level inside the lesion, which needs to be confirmed by further studies.

Elastography reflects the hardness characteristics of tissue, which is closely related to the biological characteristics of the lesion[18]. In general, the hardness of the lesion is greater and the elastic coefficient is greater. Liu Xiaoli found that there were significant statistical differences in Young's modulus and Ratio of benign and malignant thyroid nodules[19].In his research on breast cancer, LianYi found that the maximum Young's modulus was negatively correlated with the number of cells in the lesion ($r=-0.630$, $P<0.01$), and positively correlated with the content of collagen fiber ($r=0.646$, $P<0.01$)[20].The histological structure of glands in the different stages of lesions is different. The early performance is lymphocyte infiltration, thyroid follicle atrophy, then due to normal tissues are destroyed, thyroid gland appeared fibrosis. The contents of cells and fibrous tissue in different periods are different, which causes the thyroid gland tissue hardness is different[1,2].This study found that there was no statistical difference in Young's modulus and Ratio value between the HT group and the NHT group, but the hardness of the lesions in the hypothyroidism stage was significantly higher than that in the other two stages, and the Ratio value was significantly lower than that in the other two stages. It can be seen that different stages of HT not only affect the hardness of thyroid gland itself, but also have a great impact on the hardness of PTC nodules and their Ratio value.

5. Conclusion

From what has been discussed above, we learned that HT in different functional states has little influence on the two-dimensional acoustic image characteristics of PTC, and has certain influence on the hardness and blood flow of the lesion. Therefore, when we encounter suspicious PTC nodules with HT, the operator should further apply elastography, superb micro-vascular imaging, contrast-enhanced ultrasound and other technologies, and integrate the patient's laboratory examination results to make an accurate judgment of the lesion.

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