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Research

Diagnostic value of traditional Chinese medical dialectical classification in hashimoto's thyroiditis complicated with suspicious nodules

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Highlights

Currently, the commonly used methods for evaluating thyroid nodules include ultrasound and fine-needle aspiration biopsy. Due to the different diagnostic experience of doctors, there are differences in the evaluation of the nature of nodules. Secondly, the stimulation of inflammation causes thyroid cells to enlarge and deform, which is difficult to distinguish from malignant cells in cytology. Therefore, the treatment of patients with Hashimoto's thyroiditis with suspicious nodules has become a major problem. This study is based on the theory of traditional Chinese medicine and incorporated the traditional Chinese medicine syndrome differentiation into the preoperative evaluation method of Hashimoto's thyroiditis with suspicious nodules.

Abstract

Objective: To explore the diagnostic value of traditional Chinese medical (TCM) dialectical classification in Hashimoto's thyroiditis complicated with suspicious nodules. **Methods:** The clinical data of patients with Hashimoto's thyroiditis complicated with thyroid nodules in the Department of Breast and thyroid surgery of Weifang Hospital of traditional Chinese Medicine from January 2018 to December 2019 were collected. The patients were examined by 2 or more experienced TCM doctors, and the four diagnostic data were obtained, and then the relevant syndrome types of the patients were judged according to the data. According to the color Doppler ultrasonographic features of thyroid nodules, the patients who met the indication of fine needle aspiration biopsy of thyroid nodules were selected and underwent fine needle aspiration biopsy of thyroid nodules before operation. To analyze the clinical diagnostic value of that the ultrasonic mode used in this study and thyroid cytopathology Bethesda report system combine dialectical classification of traditional Chinese medicine in Hashimoto's thyroiditis complicated with suspected thyroid nodules. **Result:** A total of 89 patients with Hashimoto's thyroiditis complicated with thyroid nodules were collected. according to the ultrasonic mode, the difference between different modes was statistically significant ($P < 0.05$). The mode of color ultrasound is also related to the dialectical classification of traditional Chinese medicine. The patients with high malignant risk score are mainly qi depression and phlegm stagnation, phlegm and blood stasis, while those with low score are exuberant liver fire and heart liver yin deficiency. According to the study of different The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) classification, the dialectical classification of patients with higher TBSRTC classification was more inclined to qi depression and phlegm stagnation, phlegm and blood stasis, and there was significant difference between different classification ($P < 0.05$). **Conclusion:** Qi depression and phlegm obstruction, phlegm and blood stasis have high ultrasound malignant risk score and high TBSRTC classification grade in patients with Hashimoto's thyroiditis complicated with suspected thyroid nodules, which has important clinical diagnostic value.

Keywords: traditional Chinese medical dialectical classification, hashimoto's thyroiditis, suspicious nodules, Qi depression and phlegm obstruction, phlegm and blood stasis

***Abbreviations*:**

TCM,traditional Chinese medical; TBSRTC, The Bethesda System for Reporting Thyroid Cytopathology; HT, Hashimoto's thyroiditis.

***Competing interests*:**

The authors declare that there is no conflict of interest.

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Introduction

Hashimoto's thyroiditis (HT) is an autoimmune disease, which is characterized by chronic inflammation with autothyroid tissue as antigen, so it is also called autoimmune thyroiditis. In recent years, with the increasing incidence of HT, the incidence of HT complicated with thyroid nodules is getting higher and higher. Virchow et al research in 1863 suggested that the development of cancer begins with chronic inflammation, which can lead to tumorous transformation, such as chronic hepatitis B and liver cancer, ulcerative colitis and rectal cancer. The incidence of HT with thyroid cancer is reported to be quite different in the literature. In China, it is reported that the incidence of HT complicated with thyroid cancer is 0.6% and 23.8% [1-2], while foreign studies have reported that the incidence is between 0.5% and 38.0% [3-5]. The diagnosis and treatment of HT with thyroid nodules has become the research focus of scholars at home and abroad. At present, there are many reports in this area, but there is no unified diagnosis and treatment. Therefore, this study discusses the diagnostic value of TCM dialectical classification in HT complicated with suspicious nodules by giving full play to the advantages of TCM.

Methods

1.Clinical data

The clinical data of 147 patients with HT complicated with thyroid nodules in the department of breast and thyroid surgery of Weifang hospital of traditional Chinese medicine from January 2014 to December 2015 were collected. After the patients were treated in our hospital, the basic data, ultrasonographic features and cytopathological results of fine needle aspiration biopsy were recorded. According to the color ultrasound features of thyroid nodules, patients with thyroid nodules were selected according to the indication of thyroid fine needle aspiration biopsy. Fine needle aspiration biopsy of thyroid nodules was performed before operation, and the pathological results of fine needle aspiration biopsy were recorded. Routine pathological examination was performed after surgical treatment. Because some patients with benign nodules have a strong demand for surgery because of their psychological burden, this part of patients are also included in the study. Finally, 89 patients were treated by operation, 34 cases were confirmed as thyroid cancer by postoperative pathological results, including 2 cases of thyroid follicular carcinoma. The age of the patients ranged from 25 to 75 years old, with a median age of 45 years old. There were 66 female patients and 23 male patients.

2.Dialectical classification of traditional Chinese medicine

The patients are examined by two or more experienced TCM doctors, from which the four diagnostic data are obtained, and then the relevant syndrome types of the patients are judged according to the data.

1) Qi depression and phlegm obstruction: there are swollen lumps on both sides of the anterior larynx of the patient, which are soft and touch differently, the patient will have the feeling of neck fullness and chest tightness, like to sigh, or there is obvious string pain in the position of the chest flank. In clinic, the patient's condition will change with the change of the patient's mood. The patient's tongue coating is thin and white,and the pulse strings; 2) phlegm and blood stasis: enlarged lumps can also be seen on both sides of the anterior laryngeal nodule of the patient, which are hard to touch or have nodular sensation, the mass has not disappeared for a long time, the patient has clinical symptoms such as chest tightness and anorexia, the tongue is dark and purple, and the tongue coating is mainly thin and white and greasy, pulse string or astringent; 3) exuberant liver fire: the mass on both sides of the anterior laryngeal node of the patient is mildly or moderately enlarged, its quality is soft and smooth, the patient has clinical irritability and sweating, and the mood is mainly irritable and irritable. Facial redness, exophthalmos, finger tremor, bitter mouth, red tongue, thin yellow tongue coating, pulse string number; 4) Yin deficiency of heart and liver: the mass on both sides of the anterior larynx is large or small, the situation is different, the texture is relatively soft, the onset of the disease is slow, more by palpitation, restlessness, less sleep, easy to sweat, etc., red tongue, little or no fur, pulse string count.

3.Thyroid nodule ultrasonic characteristics (mode) scoring system

According to the definition of suspicious ultrasonic features (ultrasonic mode) proposed by professors Lewinski and Adamczewski:1) calcification foci: especially with microcalcification and other forms of calcification (such as malnutrition); no calcification indicates benign lesions; 2) shape: transverse and longitudinal shape "high > wide". Other shapes suggest benign lesions; 3) doppler ultrasound: increased irregular central blood flow, including hypoechoic lesions with no blood flow at all; peripheral subcapsular blood flow indicates benign lesions; 4) echo intensity: low echo, that is, darker than the normal thyroid echo, similar to the echo intensity of the muscles around the gland, especially the sternocleidomastoid muscle; 5) halo: disappearance of halo or uneven thickness of the

outer layer (edge) around the lesion; thin and regular halo around the lesion indicates benign lesions; 6) echo structure: mixed lesions with solid lesions and cystic parts with less than 10% volume. The mixed part of the cystic part with a volume of more than 10% and complete cystic components suggest benign lesions; 7) size: the diameter of the lesion is greater than 3cm; the diameter is smaller than 3cm indicates benign lesions; 8) margin: margin unclear and irregular, sometimes marginal infiltration; clear boundaries and rules suggest benign lesions. 9) growth rate: within 1.5 years, the lesion increased by at least 20% in both directions, that is, the volume increased by at least 50% (the diameter of the lesion in both directions was less than 10 mm-the smallest 2 mm); 10) the lymph nodes were involved: the suspected lymph nodes could be seen by ultrasound, and the minimum diameter higher than 5-8 mm.

As any single thyroid ultrasound feature can not distinguish between benign and malignant lesions, professor Lewinski and professor Adamczewski, on the basis of the above ultrasound characteristics, take the first letter of each ultrasound feature name to form mnemonic words, and rely on their own teaching experience to establish a system. The evaluation principle of the system is to add the scores and classify the lesion scores into specific groups with different malignant risks.

<table>
<tr><th colspan="3">CODE（Each feature-1 point）</th><th colspan="3">HELM（Each feature-0.5）</th><th colspan="3">AL（Each feature-3 points）</th></tr>
<tr><td>C</td><td>Calcification</td><td rowspan="4">The highest score is 4 points</td><td>H</td><td>Halo</td><td rowspan="4">The highest score is 2 points</td><td rowspan="2">A</td><td rowspan="2">Growth rate</td><td rowspan="4">The highest score is 6 points</td></tr>
<tr><td>O</td><td>Shape</td><td>E</td><td>Echo structure</td></tr>
<tr><td>D</td><td>Doppler</td><td>L</td><td>Size</td><td rowspan="2">L</td><td rowspan="2">Lymph node involvement</td></tr>
<tr><td>E</td><td>Echo intensity</td><td>M</td><td>Boundary</td></tr>
</table>

Note: ultrasound mode low risk: 0-< 4 points; ultrasound mode medium risk: ≥ 4 < 7 points; ultrasound mode high risk: ≥ 7 points

4.Basis of cytopathological diagnosis

The cytopathological diagnosis of fine needle aspiration biopsy in this study is based on TBSRTC of Cibas and Ali50:

Diagnostic classification	Malignant risk（%）
I. No diagnostic significance or unsatisfactory selection of materials	1-4
II. Benign	0-3
III. An atypical or unknown follicular lesion of unknown meaning	5-15
IV. Follicular tumor or suspected follicular tumor	15-30
V. Suspected malignant	60-75
VI. Malignant	97-99

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5.Statistical analysis

SPSS19.0 statistical software was used for statistical analysis. The experimental data were expressed as mean ± standard deviation. Chi-square test was used for the comparison of counting data between groups. When $T < 1$ or $n < 40$, the difference was statistically significant.

Result

1.Correlation analysis of TCM syndrome differentiation combined with color doppler ultrasonography in HT with thyroid nodules.

In this study, 89 patients with HT complicated with thyroid nodules were collected. All patients were examined by ultrasonography before operation to evaluate the nature of thyroid nodules.There were 35 cases of low risk model, including qi depression and phlegm obstruction (2 cases), exuberant liver fire (15 cases) and heart-liver yin deficiency (18 cases). 2 cases of thyroid carcinoma were confirmed by postoperative pathology (dialectical syndrome of qi depression and phlegm obstruction).There were 24 cases of moderate risk model, including qi depression and phlegm stagnation (5 cases), phlegm and blood stasis (4 cases), exuberant liver fire (10 cases) and heart-liver yin deficiency (5 cases). 9 cases of thyroid carcinoma were confirmed by postoperative pathology (5 cases of qi stagnation and phlegm stasis, 3 cases of phlegm stasis and 1 case of exuberant liver fire).Here were 30 cases of high risk model, including qi depression and phlegm stagnation (14 cases), phlegm and blood stasis (10 cases), exuberant liver fire (4 cases) and heart-liver yin deficiency (2 cases). 22 cases of thyroid carcinoma were confirmed by postoperative pathology (10 cases of qi stagnation and phlegm stasis, 9 cases of phlegm stasis and 3 cases of exuberant liver fire). The color Doppler ultrasound model used in this study is of diagnostic value to evaluate suspicious nodules, and the differences between different modes are statistically significant ($P < 0.05$). There is also a correlation between the mode of color ultrasound and the syndrome differentiation of traditional Chinese medicine. The dialectics of patients with high malignant risk score were mainly qi depression and phlegm stagnation, phlegm and blood stasis, while those with low score were exuberant liver fire and heart liver yin deficiency. (Tables 1,2)

Ultrasonic mode	Is the postoperative pathological result of thyroid carcinoma?		Total	Diagnosis rate
	Yes	No		
Low risk	2	33	35	6.1%
Moderate risk	9	15	24	37.5%
high risk	23	7	30	76.7%
Total	34	55	89	P < 0.05

Table 1 Evaluation of diagnostic value of suspicious nodules by color doppler ultrasonography

Syndrome differentiation	Ultrasonic mode			Total	P 值
	Low risk	Moderate risk	High risk		
Stagnation of qi and phlegm	2 (9.5%)	5 (23.8%)	14 (66.7%)	21	$P < 0.001$
Phlegm and blood stasis	0 (0%)	4 (28.6%)	10 (71.4%)	14	
Exuberant liver fire	15 (51.8%)	10 (34.5%)	4 (13.8%)	29	
Yin deficiency of heart and liver	18 (72%)	5 (20%)	2 (8%)	25	
Total	35	24	30	89	

Table 2 Diagnostic value of different dialectical types of TCM in the evaluation of suspicious nodules under the mode of color ultrasound

2.Correlation Analysis of TCM syndrome differentiation combined with TBSRTC Classification in HT complicated with suspected nodules.

In this study, the patients with VI malignant results and V suspected malignancy were combined into one group. Type I had no diagnostic significance or unsatisfactory samples. There were 8 patients, including 1 case of dialectical stagnation of qi and phlegm, 7 cases of exuberant liver fire, and only 1 case of thyroid cancer confirmed by pathology after operation (stagnation of qi and phlegm). A total of 22 patients with type II benign diagnosis were classified, including exuberant liver fire (12 cases) and heart-liver yin deficiency (10 cases). All of them were proved to be benign tumors (exuberant liver fire and heart-liver yin deficiency). A total of 13 patients with type III atypical or unknown follicular lesions were diagnosed as phlegm and blood stasis (2 cases), exuberant liver fire (5 cases) and heart-liver yin deficiency (6 cases). Postoperative pathology confirmed thyroid cancer in 2 cases (phlegm and blood stasis). A total of 17 patients with type IV follicular tumor or suspected follicular tumor were diagnosed as qi depression and phlegm stagnation (2 cases), phlegm and blood stasis (2 cases), exuberant liver fire (7 cases) and heart-liver yin deficiency (6 cases). There were 5 patients with thyroid carcinoma confirmed by pathology after operation. Among them, 2 cases were follicular carcinoma. A total of 29 patients with suspected malignancy and type VI malignancy were classified as qi depression and phlegm stagnation (17 cases), phlegm and blood stasis (10 cases) and heart-liver yin deficiency (2 cases). There were 29 patients with thyroid cancer confirmed by pathology after operation. Studies have shown that the use of TBSRTC is valuable in the diagnosis of suspicious nodules, and the dialectical types of patients with higher classification are more inclined to qi depression and phlegm stagnation, phlegm and blood stasis, and there are statistical differences among different classification. (Tables 3, 4)

TBSRTC classification	Is the postoperative pathological result of thyroid carcinoma?		Total	Diagnosis rate
	Yes	No		
I	1	7	8	12.5%
II	0	22	22	100%
III	2	11	13	15.4%
IV	5	12	17	29.4%
V、VI	26	3	29	89.66%
Total	34	55	89	$P < 0.05$

Table 3 TBSRTC classification to evaluate the diagnostic value of suspicious nodules

Syndrome differentiation	BSRTC classification					P 值
	I 、II	III	IV	V、VI	Total	
Stagnation of qi and phlegm	1 （5%）	0 （0%）	2 （10%）	17 （85%）	20	$P < 0.001$
Phlegm and blood stasis	0 （0%）	2 （14.3%）	2 （14.3%）	10 （71.4%）	14	
Exuberant liver fire	19 （61.3%）	5 （16.1%）	7 （22.6%）	0 （0%）	31	
Yin deficiency of heart and liver	10 （41.7%）	6 （25%.0）	6 （25.0%）	2 （8.3%）	24	
Total	30	13	17	29	89	

Table 4 Diagnostic value of different dialectical types of traditional Chinese medicine to evaluate suspicious nodules in BSRTC classification

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Discussion

HT with suspected nodules is difficult to distinguish from simple thyroid carcinoma in clinic. Blind operation may lead to a series of complications such as hypothyroidism. At present, the commonly used evaluation methods of thyroid nodules include ultrasound and fine needle aspiration biopsy. Due to the different diagnostic experience of doctors, there are also differences in the evaluation of the nature of thyroid nodules. Secondly, the stimulation of inflammation leads to the enlargement and deformation of thyroid cells, which is difficult to distinguish from malignant cells in cytology. Therefore, the treatment of patients with HT complicated with suspicious nodules has become a major problem. HT in traditional Chinese medicine belongs to the category of "gall disease" and "gall tumor" according to the characteristics of diffuse enlargement and hardness of thyroid gland. TCM believes that the etiology of gall disease is closely related to emotional injury, diet, soil and water inappropriateness and physical factors. Improper diet and inappropriate soil and water will not only affect the function of the spleen and stomach, make the spleen lose its healthy transport, unable to transport water and dampness, gather and produce phlegm, but also lead to poor operation of qi and blood, qi stagnation, phlegm, blood stasis and gall in front of the neck. Therefore, in this study, based on the theory of traditional Chinese medicine, TCM syndrome differentiation was incorporated into the preoperative evaluation method of Hashimoto's thyroiditis with suspicious nodules, and the accuracy of preoperative diagnosis was further improved by the combination of traditional Chinese and western medicine.

Ultrasound is the most sensitive method for the examination of thyroid lesions [6]. According to the literature, the risk of diagnosing thyroid cancer is 0.5% -13% [7,8-10]. Many reports have shown that the risk of malignant lesions detected by ultrasound has nothing to do with the number of single or multiple masses [11,12]. However, recent reports have shown that multiple nodular goiter has a higher risk of canceration [13]. Solid hypoechoic lesions with increased blood flow and irregular boundaries need to be differentiated from focal thyroiditis, such as Hashimoto's thyroiditis with thyroid nodules. Because this kind of chronic focal thyroiditis is very common, ultrasonography often shows solid high-echo star lesions, surrounded by hypoechoic tissue, and sometimes only around thin linear hypoechoic areas similar to thyroid lesions, commonly seen in HT. Some scholars believe that if we can accurately identify these ultrasound features, we can almost rule out the possibility of cancer[14,15]. Some scholars have analyzed the syndrome differentiation of ultrasound and TCM, suggesting the clinical significance of the combined application of the two methods in Hashimoto's thyroid cancer [16]. In this study, ultrasonic mode was used to evaluate HT with suspicious nodules before operation,the results showed that there were statistical differences among different ultrasonic modes. The two types of qi depression and phlegm stagnation, phlegm and blood stasis have higher diagnostic value in malignant nodules.

In addition to ultrasound examination, most scholars believe that fine needle aspiration biopsy of thyroid gland is the basic step to determine whether patients should be operated or not [17-19]. However, cytological examination has its own limitations, according to TBSRTC classification, even for a benign lesion and based on a sufficient number of normal thyroid follicular cells to make a diagnosis, due to inevitable errors in the operation or defects in the tissue itself, the puncture results are 1% Mel 11% false negative [20-21]. In this study, TCM syndrome differentiation was added to the puncture pathological diagnosis for the first time, and the results showed that there were statistical differences among different TBSRTC classification, and the results also showed that qi depression and phlegm stagnation, phlegm and blood stasis had high diagnostic value in malignant nodules.

In this study, TCM syndrome differentiation was incorporated into the preoperative evaluation system for thyroid nodule surgery. TCM syndrome differentiation combined with thyroid nodule ultrasonic mode scoring system and TBSRTC have important clinical significance for the diagnosis of HT with thyroid nodules. Combined application can effectively help clinicians to improve the diagnosis of suspicious nodules and provide the best treatment for patients.

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