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Ultrasound-aided Follow-up of Patients with Hashimoto's Thyroiditis and Accompanying Nodules for Papillary Thyroid Carcinoma

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Abstract

Objectives: To monitor the natural course of thyroid nodules in patients with Hashimoto's thyroiditis with ultrasound during follow-up. Methods: The clinical data about the 192 patients who were treated for HT at the First Affiliated Hospital of Jinan University from January 2017 to December 2019 were collected. There were 89 patients with accompanying nodules. All the patients underwent systematic ultrasound examinations. Ultrasonography (US) was performed again after treatment and the results were compared with those found before. Results: At initial diagnosis, 14 nodules (14.43%) were diagnosed as papillary thyroid carcinoma (PTC) with fine-needle aspiration biopsy (FNAB). After a follow-up period of 6 to 18 months, 22 new nodules were observed, and size increase was found in 8 nodules. Nine nodules were confirmed as PTC with FNAB. The proportion of TI-RADS 4 and 5 at initial diagnosis was similar to that at the end of follow-up (62.3% vs 64.9%, P > 0.05). The incidence of PTC was slightly higher during follow-up than that at initial diagnosis (20.2% vs 14.4%), however, the difference was not statistically significant (P > 0.05). Conclusion: The prevalence of PTC in patients with HT is relatively higher than that in the general population. US can help observe patients with HT closely for new growths of PTC during follow-up.

Keywords

Hashimoto's thyroiditis; Thyroid cancer; Papillary thyroid carcinoma; Fine-needle aspiration biopsy; Ultrasonography.

1. Introduction

Hashimoto's thyroiditis (HT), also known as chronic lymphocytic thyroiditis, is not only one of the most common diffusive thyroid diseases, but also one of the most common autoimmune disorders. Researchers have begun to pay attention to the correlation between HT and thyroid cancer because chronic inflammation is believed to predispose patients to neoplastic transformation and autoimmune diseases associated with various malignancies. Papillary thyroid carcinoma (PTC) is the most common type, making up 80% to 90% of all thyroid cancer cases. Many studies aim to explore the association between PTC and HT and find out whether coexisting HT will affect the clinicopathological characteristics and prognosis of PTC.

Studies find that the incidence of PTC in patients with HT is higher than that in the general population and that HT is associated with significantly increased risk of developing PTC [1, 2]. The meta-analysis by Lai et al. [3] reports that the incidence of PTC in patients with HT is 1.12% to 40.11%. HT is frequently accompanied by high titers of thyroid peroxidase antibodies (TPOAb) and thyroglobulin antibodies (TgAb) in the serum. As the function of the thyroid decreases in the late

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stage, the level of thyroid-stimulating hormone (TSH) in the serum increases because of the negative feedback mechanism [4]. Elevated Anti-TPO antibodies or TSH levels are associated with an increased incidence of thyroid cancer in patients with HT. The risk of PTC will increase with the serum TSH level even if the latter is within the normal range [5, 6]. Although HT is a high-risk factor for PTC, it can help inhibit the formation or growth of tumors. Clinical pathology reveals that lymphocytes, macrophages, mast cells and other autoimmune inflammatory cells often infiltrate around thyroid cancer tissues. Patients with only thyroid cancer have a poorer prognosis than those with both thyroid cancer and HT. Cooccurrence of thyroid cancer and HT is more common in females and the tumors are characterized by multiple foci, early stage, less cervical lymph node and extrathyroidal invasion, and low recurrence rate [7].

Although ultrasonography (US) is the preferred imaging method for distinguishing between benign and malignant thyroid nodules in the context of HT, however, a considerable number of malignant thyroid nodules is atypical on ultrasonograms. Since chronic inflammation lasts for prolonged periods, the degree of interstitial thyroid fibrosis is different in different stages of HT. The thyroid gland may present diffuse nodular or grid-like changes, leading to differences between ultrasonograms. If a single or multiple thyroid nodules are formed in the context of HT, their sonographic features may be variable and atypical, and may overlap with those of malignant nodules, which may lead to neglect of malignant thyroid nodules, especially small thyroid cancer, while making a diagnosis [8]. Progression of HT leads to not only increased roughness of the gland texture and widely distributed hyperechoic septations on ultrasonograms, but also formation of micronodules, increasing difficulties in differentiation between benign and malignant nodules.

Studies have been conducted to analyze the manifestations of PTC on ultrasonograms in patients with HT and assess the diagnostic capabilities of US, however, most of them are cross-sectional ones. This study screens patients with HT for neglected PTC by analyzing the changes in the US features of thyroid nodules during follow-up, aiming to increase the accuracy of PTC diagnosis in patients with HT by evaluating the prevalence of PTC in patients with HT at the time of initial diagnosis and that during follow-up, and exploring the value of US in diagnosing malignant thyroid nodules in the context of HT during follow-up.

2. Materials and Methods

2.1 Patients

There were 192 patients who were diagnosed with HT for the first time in the First Affiliated Hospital of Jinan University from January 2017 to December 2019 and all of them were enrolled in this study. Eighty-nine of them were found with 97 accompanying thyroid nodules, consisting of 73 females and 16 males whose age ranged from 21 to 63 years with an average of 38.2 years. Diagnosis of HT was confirmed in all the patients with clinical manifestations and laboratory tests. After clinical treatment, all the patients underwent US during follow-up which varied from 6 months to 18 months.

2.2 US and follow-up

US was performed using Philips IU Elite ultrasound system (Philips Ultrasound System, Netherlands) with a L12-5 transducer and TOSIBA Aplio 500 ultrasound system (Toshiba Medical Systems Corporation, Tokyo, Japan) with a L14-5 transducer. The patient was in the supine position with the thyroid being fully exposed. The thyroid and the lymph nodes in the neck were routinely examined with ultrasound, and echo and blood signals inside the thyroid gland were observed. The process focused on detecting suspicious thyroid nodules and recording their features, including their specific location, size, echo signals, texture, edges, aspect ratio, calcification, association with the thyroid capsules, internal blood supply, and lymph node metastases in the neck. The nodules were scored and classified with the Thyroid Imaging, Reporting and Data System (TI-RADS) proposed by the

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American College of Radiology [9, 10]. They were then compared during follow-up to analyze their differences in US features and TI-RADS score.

2.3 Fine-needle aspiration biopsy (FNAB)

2.3.1 Indications

FNAB was performed according to guidance by the ACR TI-RADS Committee [9] on patients with: 1) TI-RADS 3 nodules with a diameter of more than 2.5 cm; 2) TI-RADS 4 nodules with a diameter of more than 1.5 cm; 3) TI-RADS 5 nodules with a diameter of more than 1.0 cm; 4) nodules which increased during follow-up by at least 2 mm and 20% in two of the three dimensions (width, height, anteroposterior dimension), or whose volume increased during follow-up by at least 50%; or 5) nodules whose TI-RADS score increased during follow-up.

2.3.2 Procedure

FNAB was performed using TOSIBA Aplio 500 ultrasound system (Toshiba Medical Systems Corporation, Tokyo, Japan) with a L14-5 transducer. The patient was lying in a supine position with the neck higher than the rest of the body to fully expose the thyroid gland. He or she was required not to swallow and cough. The probe was hold in the aspirator' left hand to lead the 23G needle which was in the right hand to puncture a suspicious nodule without negative pressure and repetitively at different points (usually 2 to 4 points). Four to eight smears were obtained and fixed immediately with 95% ethanol before they were sent to the cell laboratory for examination. When the patients had multiple suspicious nodules, two nodules which met the requirements for FNA and had higher TI-RADS scores than the rest were punctured.

2.3.3 Cytopathological diagnostic categories

There are six Bethesda diagnostic categories [11]: Bethesda I (nondiagnostic or unsatisfactory, ND), Bethesda II (benign), Bethesda III (atypia of undetermined significance or follicular lesion of undetermined significance, AUS/FLUS), Bethesda IV (follicular neoplasm or suspicious for a follicular neoplasm, FN/SFN), Bethesda V (suspicious for malignancy, SM) and Bethesda VI (malignant). Another FNAB was performed on patients with Bethesda I nodules at least 6 months later during follow-up.

2.4 Statistical analysis

SPSS version 19.0 was used to conduct statistical analysis. The measurement data were expressed as means ± standard deviations, while the count data were expressed as percentages (%). Chi-squared test was used for comparison. A P value of less than 0.05 was considered to indicate statistical significance.

3. Results

3.1 Nodules at initial diagnosis

A total of 97 nodules were observed in 89 of the 192 HT cases at initial diagnosis, and 63 of them (63/97, 64.9%) were TI-RADS 4 and 5 nodules. FNAB was performed on the 57 nodules which met the requirements, and 14 (14/97, 14.43%) were diagnosed as PTC. See Table 1 for details.

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Table 1 Patients and thyroid nodules at initial diagnosis

	Cases	FNAB (n)	PTC (n)
Patients	**89**	**55**	**13**
Patients with single nodules	81	51	12
Patients with multiple nodules	8	4	1
Nodules	**97**	**59**	**14**
TI-RADS 1	7	0	/
TI-RADS 2	18	0	/
TI-RADS 3	9	4	0
TI-RADS 4	55	37	9
TI-RADS 5	8	8	5

TI-RADS, the Thyroid Imaging Reporting and Data System; FNAB, fine-needle aspiration biopsy; PTC, papillary thyroid carcinoma.

3.2 Changes to nodules at the end of follow-up

After follow-up which ranged from 6 to 18 months, the TI-RADS score of 6 nodules increased from 4 to 5, and 4 of the 6 nodules were diagnosed as PTC with FNAB. The TI-RADS score of one nodule decreased from 5 to 3. During follow-up, the diameter of 8 nodules (8/97, 8.2%) increased by 23.08% and 2 of them was diagnosed as PTC with FNAB. Twenty-two new nodules were observed in 20 patients with HT, including 5 of TI-RADS 1, 4 of TI-RADS 2, 2 of TI-RADS 3, 6 of TI-RADS 4 and 5 of TI-RADS 5. FNAB was performed on the 7 new nodules who met the requirements and revealed 3 cases of PTC (13.6%). Two TI-RADS-3 and 3 TI-RADS-4 nodules disappeared during follow-up. See Table 2 for details.

The incidence of thyroid nodules during follow-up was higher than that at initial diagnosis (56.4% vs 46.4%, $P < 0.05$). The proportion of TI-RADS 4 and 5 nodules during follow-up was similar to that at initial diagnosis (62.3% vs 64.9%, $P > 0.05$). The incidence of PTC was slightly higher during follow-up than that at initial diagnosis, however, the difference was not statistically significant (20.2% vs 14.4%, $P > 0.05$).

Table 2 Changes to thyroid nodules during follow-up

	New nodules (n)	Disappeared nodules (n)	Size Increase (n)	TI-RADS score increase (n)	FNAB (n)	PTC (n)
TI-RADS 1	5	0	3	0	0	/
TI-RADS 2	4	0	2	0	0	/
TI-RADS 3	2	2	1	0	1	0
TI-RADS 4	6	3	1	6	9	6
TI-RADS 5	5	0	1	0	6	3
Total	**22**	**5**	**8**	**6**	**25**	**9**

TI-RADS, the Thyroid Imaging Reporting and Data System; FNAB, fine-needle aspiration biopsy; PTC, papillary thyroid carcinoma.

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4. Discussion

In this study, the US features of thyroid nodules in patients with HT and changes to the TI-RADS scores were recorded during follow-up. There were 22 new nodules and 9 newly confirmed PTC cases. The TI-RADS score of 6 nodules increased from 4 to 5. The size of 8 nodules increased. After a follow-up period of 6 to 18 months, the incidence of nodules increased significantly (56.4% vs 46.4%, $P < 0.05$), while that of PTC increased slightly (20.2% vs 14.4%) and the difference between the incidence of PTC at initial diagnosis and that after follow-up was not statistically significant ($P > 0.05$).

The meta-analysis by Lai et al. [3] on 6 FNAB studies (25,777 patients) demonstrated that the incidence of PTC in HT patients with accompanying nodules ranged from 0.12% to 20.87% with an average of 6.46%. After excluding possible abnormal research results, they found that the average incidence was 3.58%. In this study, the incidence of PTC was 14.4% at initial diagnosis and 20.2% after a follow-up period of 6 to 18 months. It seems that immune responses to chronic inflammation are associated with tumorigenesis. The microenvironment inside the thyroid gland in patients with HT is characterized by lymphocytic infiltration and presence of other immunocompetent cells and soluble mediators (including chemokines, cytokines, and growth factors), which consist of a major part of cell transformation and tumor progression. This supports the idea that tumor development may involve the molecular mechanism of inflammation, or even the immune system in the late stage [12].

HT is a complicated medical condition characterized by diffuse lymphocytic infiltration that causes progressive damage to the thyroid tissue. Thyroid nodules in the context of HT may have atypical ultrasound characteristics, and there may be similarities in morphology, margins, and echo signals between benign and malignant lesions. In addition, some US features of atypical small or early-stage malignant thyroid nodules with no signs of infiltration are the same as those of benign nodules, such as, normal morphology and well-defined boundaries, affecting the accuracy of US in the diagnosis of PTC. Boi et al. [13] followed-up 241 patients with nodular HT for 1 to 6 years with a sex- and age-matched group of 161 patients with nodular goiter as the control group. During follow-up, the incidence of new suspicious malignant nodules was 22% (6/28) in the group of nodular HT, higher than that in the control group (12/161, 7.4%; $P < 0.001$). In this study, 22 new nodules were observed. FNAB were performed on the 7 new nodules which met the requirements and confirmed 3 cases of PTC (13.6%). The incidence of PTC in this study is lower than that in Boi et al.'s [13] study. One potential cause may be that our follow-up period is shorter than theirs. Tuttle et al. [14] conducted multiple consecutive ultrasound measurements on 290 PTC patients who underwent active surveillance at a tertiary referral center and found the volume of 12% of PTC increased by more than 50% after a median follow-up period of 25 months. In this study, 2 nodules whose size increased were diagnosed as PTC and accounted for 9.1% (2/22) of all confirmed cases during follow-up, which is consistent with previous reports. Although thyroid cancer is not as harmful to the patient's health as other malignant tumors, early detection of lesions and reasonable choice of treatment plans are of great significance to prognosis and health improvement.

Two nodules of TI-RADS 3 and 3 of TI-RADS 4 disappeared during follow-up in this study. The nodules that disappeared are all small nodules and one possible cause may be misdiagnosis of focal hyperplasia as a nodule at initial diagnosis. HT does not only increase the roughness of the gland's texture and cause extensive hyperechoic septations on ultrasonograms, but also lead to formation of micronodules. An elevated TSH level will stimulate proliferation of thyroid follicular epithelial cells, increase the density of follicles, and cause thyroid interstitial fibrosis which will lead to formation of lobular septations and accompanying lymphocytic infiltration. Fibrous hyperplasia at different degrees has different consequences: mild hyperplasia can lead to thin fibrous septations, while severe hyperplasia can cause thick fibrous septations and accompanying hyalinization. Fibrous septations encase the thyroid parenchyma and form Hashimoto's nodules, which are essentially HT. One pathological characteristic of Hashimoto's nodules is that lymphocytic infiltration is more severe than infiltration in the other areas in the lesion. The mesenchymal components (collagen fiber hyperplasia)

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of Hashimoto's nodules can absorb more ultrasound waves than other cells, therefore, the nodules may be posteriorly attenuated and hypoechoic when they have more mesenchymal components than cell components or when the amount of the two components are similar, making diagnosis subject to US performers [15].

There are some limitations in this study. One is that the sample is small. A larger sample will increase the accuracy of the results in this study. The other one is that the follow-up is short. A longer follow-up period should be a focus for future research.

5. Conclusion

The prevalence of PTC in patients with HT is relatively higher than that in the general population. US can help observe patients with HT closely for new growths of PTC during follow-up.

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