“Onion Skin-like Sign” in Thyroid Ultrasonography: A Characteristic Feature of Benign Thyroid Nodules

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Background: Some ultrasonographic (US) signs overlap between benign and malignant nodules. The purpose of this study was to raise a special US sign of benign thyroid nodules, termed the “onion skin-like sign.”

Methods: Twenty-seven patients with 27 nodules who shrank naturally and the “onion skin-like sign” appeared on the final US images were enrolled in the study. The ultrasound characters and risk stratifications at the start and end of observation were compared. Then, thirty goiters with fibrosis and thirty papillary thyroid carcinomas (PTC) were randomly selected from the database of our hospital, matched the sizes of 27 nodules at the end point of observation. The differences of “onion skin-like sign” between the two groups were analyzed.

Results: The average duration of follow-up of 27 nodules was 24.0 ± 12.2 months (range, 12–65 months). At the end of the follow-up, the size of the nodules decreased on average by 1.26 ± 0.82 cm (range, 0.3–3.4 cm) and calcification was found in 21 nodules, compared with only 2 nodules with calcification at the start of the follow-up. In addition, only negligible or no blood flow signal could be detected at the periphery of all the nodules and 100% (27/27) were high suspicion at the end of observation. In matched groups, all PTC showed high suspicion of malignancy, 18/30 (60%) goiters with fibrosis were high suspicion and 11/30 (37%) were intermediate suspicion. Twenty-two patients in the group of nodular fibrosis presented “onion skin-like sign,” which was not shown in any patient of PTC group. The sensitivity, specificity, positive predictive value, and negative predictive value of “onion skin-like sign” in predicting nodular goiter with fibrosis were 73.3%, 100%, 100%, and 78.9%, respectively.

Conclusions: The “onion skin-like sign” was a characteristic US feature of benign thyroid nodules detected in the follow-up of thyroid nodules. It is useful to differentiate PTCs and nodular goiters with fibrosis.

Key words: Diagnosis; Nodular Goiters; Papillary Carcinoma; Thyroid; Ultrasound

INTRODUCTION

Thyroid nodules are quite common. Approximately 4–8% of adults are diagnosed with thyroid nodules by palpation while 40–50% are diagnosed by ultrasound. However, approximately 5.0–6.5% of these nodules are malignant. In recent years, the incidence of thyroid carcinoma is increasing fast.[1-3] Therefore, the key for the diagnosis and treatment of thyroid nodules is to identify the very few malignant nodules from the tremendous amount of thyroid nodules.[4]

As is known to us, microcalcifications, hypoechoogenicity, increased nodular vascularity, infiltrative margins, and taller than wide dimensions on the transverse view are suspicious ultrasonographic (US) features of malignant nodules.[5] However, some benign nodules can also display one or more of the above features.[6] In other words, some US signs overlap between benign and malignant nodules. The purpose of the study was to raise a special US sign of benign thyroid nodules, termed “onion skin-like sign,” which can help us recognize some benign nodules with suspicious malignant US features. The “onion skin-like sign” was defined as...
a typical layered structure with hypoechoicogenicity and hyperechoicogenicity alternatively distributing from the edge to the center of the nodule.

**Methods**

This study was approved by the Ethics Committee of Peking Union Medical Hospital, and written informed consents were obtained from all patients to use their data in this study. The study included two parts. In the first part, we reviewed the outpatient database including patients who were diagnosed as benign thyroid nodules from June 2009 to January 2015 and 27 nodules in 27 patients were enrolled in the study. The inclusion criteria were that nodules shrank naturally and displayed the “onion skin‑liked sign” on the final US image during US follow‑up. Eighteen cases demonstrated normal follicles and fiber connective tissue pathologically by fine needle aspiration (FNA) or were diagnosed as a nodular goiter with fibrosis by surgical pathology; others were diagnosed benign nodules by clinical manifestations. In the second part, we randomly selected 30 goiters with fibrosis and thirty papillary thyroid carcinomas (PTC) from the inpatient database at the same period, taking the size of 27 nodules at the end point of observation as the matched condition. The differences of “onion skin‑liked sign” and risk stratification between the two groups were analyzed.

Conventional US imaging scans were obtained using a Philips iU22 scanner (Philips Medical Systems, Bothell, WA, USA) with a 5–12 MHZ linear transducer. The images were obtained under optimum instrument conditions. Standard machine settings were used with a mechanical index of 0.05–0.08, compression of 33–35, and dynamic spatial reconstructor middle. Once set, the US parameters remained unchanged in each patient. Doppler US was performed to evaluate the vascularity of the nodule. Observation began at the first US examination of the thyroid nodule and ended at the appearance of “onion skin‑liked sign.” The nodule’s position, size, shape, margin, short‑axis diameter/long‑axis diameter ratio, echogenicity, calcification, and blood flow were recorded with details. The blood flow distribution of the lesion was categorized into four levels as follows: Level 0 - no blood flow signal was detected in or around the nodule; Level 1 - most of the blood flow was detected around the nodule with few blood flow signals or no blood flow signal in the nodule; Level 2 - blood flow was detected around and in <1/2 of the nodule; and Level 3 - colored blood flow was detected in more than 1/2 of the nodule. By comparing the maximum diameter change in the follow‑up visits of one nodule, we assumed that if two continuous examinations of one nodule were conducted within 3 months and the diameter change was 1–2 mm, the result was calculated as measuring error and was not recorded. The nodules were also classified as solid or predominantly solid, with either peripheral blood flow or no blood flow. All nodules were defined as one of the four risk stratifications based on the “2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer.”

**Results**

Of all the 27 patients (overall mean age, 50.5 years; range from 32 to 67 years), there were 22 women and 5 men. Among 27 thyroid nodules, 16 were located in the left lobe (59%) and 11 were located in the right lobe (41%). The mean number of US examinations performed for one nodule was 3.7 ± 1.4 (range, 2–8) within 12–65 months of follow‑up (average, 24.0 ± 12.2 months). At the end of the follow‑up, the size of the nodules decreased on average by 1.26 ± 0.82 cm (range, 0.3–3.4 cm). The US features of the nodules are shown in Table 1 and the “onion skin‑liked sign” is shown in Figures 1–3.

Twenty‑seven patients were classified into three groups according to the duration of the follow‑up visits. The first

| Ultrasonic features | Start of observation (n = 27) | End of observation (n = 27) |
|---------------------|-----------------------------|-----------------------------|
| Maximal diameter in cm*, mean ± SD | 2.10 ± 0.86 | 1.05 ± 0.49 |
| Shape, n (%) | | |
| Regular | 27 (100) | 20 (74) |
| Irregular | 0 | 7 (26) |
| Margin*, n (%) | | |
| Defined | 27 (100) | 18 (67) |
| Ill‑defined | 0 | 9 (33) |
| Internal components*, n (%) | | |
| Cystic or predominantly cystic | 18 (67) | 0 |
| Solid or predominantly solid | 9 (33) | 27 (100) |
| Echogenicity*, n (%) | | |
| Isoechoic | 10 (37) | 2 (7) |
| Hypoechoic | 17 (63) | 25 (93) |
| S/L ratio*, n (%) | | |
| ≥1 | 0 | 2 (7) |
| <1 | 27 (100) | 25 (93) |
| Calcification* | | |
| No calcification | 25 (93) | 6 (22) |
| Calcification | 2 (7) | 21 (78) |
| Color doppler*, n (%) | | |
| Level 3 | 4 (15) | 0 |
| Level 2 | 6 (22) | 0 |
| Levels 1 and 0 | 17 (63) | 27 (100) |
| Risk stratification*, n (%) | | |
| High suspicion | 0 | 19 (70) |
| Intermediate suspicion | 3 (11) | 8 (30) |
| Low suspicion | 12 (44) | 0 |
| Extremely low suspicion | 12 (44) | 0 |

*P<0.05; †S/L ratio: Short‑axis diameter/long‑axis diameter at a cross‑sectional ultrasound image. US: Ultrasonic.
and second group received more than 1 year of follow-up. Within the year before the last US examination (the end of observation), the first group underwent US examination while the second group did not undergo US examination. The third group received <1 year of follow-up. The maximum diameter of the nodules in each group was calculated at the final US examination, within the year before the last US examination, and more than 1 year before the last US examination. The results are shown in Figure 4.

In matched groups, there were 8 male and 22 female patients in goiters with fibrosis (50.3 ± 12.5 years) and PTC groups (45.5 ± 9.6 years), respectively. The size of benign nodules was 1.08 ± 0.30 cm, and that in PTC group was 1.06 ± 0.29 cm; no statistically significant difference was found between the two groups (P > 0.05). All PTC patients showed high suspicion of malignancy, 18/30 (60%) goiters with fibrosis were high suspicion, 11/30 (37%) were intermediate suspicion, and 1/33 (3%) were low suspicion [Table 2]. Twenty-two patients in the group of nodular fibrosis presented “onion skin‑liked sign,” which was not shown in any patient of PTC group. Moreover, there was statistically significant difference between the two groups (P < 0.05). The sensitivity, specificity, positive predictive value, and negative predictive value of “onion skin‑liked sign” in predicting nodular goiter with fibrosis were 73.3%, 100%, 100%, and 78.9% respectively.

**DISCUSSION**

US is the preferred imaging method for thyroid nodular lesions and is highly sensitive and specific in identifying benign and malignant thyroid nodules. Some nodules show typical benign features, the most common of which include the “comet tail” and “honeycomb sign/sponge sign.” However, some nodules do not display typical benign or malignant features, and a great number of goiters with fibrosis were evaluated as malignant nodules by mistake. Hence, how to evaluate such nodules has become an issue of concern.

The natural history of benign nodular goiter is largely variable and unpredictable in a given patient because no specific predictive growth parameters exist. The main pathological process of goiters is that proliferation and degeneration occur alternatively in thyroid follicles for a long period, thereby facilitating the proliferation of fibrous tissues in the thyroid. In addition, lobules or follicles full of colloidsh are often surrounded by fibrous tissues and the fibro‑capsule surrounding the nodule may reduce the blood supply of some follicles, resulting in necrosis, hemorrhage, cyst formation, scar formation, and calcification of follicles. This process can be clearly imaged with US. Hyperechogenicity corresponds to the interface between the fibrous tissues and lobules or follicles and the layer structure formed as a result of degeneration.

At follow-up observation, a decrease in nodule size is a feature of benign nodules. In our study, the size of all nodules in the three groups decreased. At the start of the
According to the guideline of American Thyroid Association (2015 version), all thyroid nodules should be evaluated risk stratification and make a decision of FNA.

In conclusion, the “onion skin‑liked sign” was a characteristic US sign of benign thyroid nodules detected in the follow‑up of thyroid nodule imaging. It is useful to differentiate PTC and goiter with fibrosis.

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**Conflicts of interest**

There are no conflicts of interest.

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