Papillary thyroid carcinomas are highly obscured by inflammatory hypoechoic regions caused by subacute thyroiditis: a longitudinal evaluation of 710 patients using ultrasonography

Eijun Nishihara, Takumi Kudo, Mitsuru Ito, Shuji Fukata, Mitsushige Nishikawa, Hirotoshi Nakamura, Nobuyuki Amino and Akira Miyauchi

Kuma Hospital, Center for Excellence in Thyroid Care, Kobe, Japan

Abstract. Subacute thyroiditis is a self-limited inflammatory disease and very few patients undergo ultrasonographic re-examination if no nodules are found at the initial examination. The objective of the study was to assess the diagnostic accuracy of ultrasonography in detecting nodular lesions in patients with subacute thyroiditis. We conducted a longitudinal study involving 710 patients with subacute thyroiditis who underwent ultrasonographic examinations in a single center between 2008 and 2018. These examinations were performed at initial diagnosis and during follow-up, with subsequent evaluation of nodules using fine needle aspiration cytology. Ultrasonographic examination used for the initial screening of thyroid nodules in patients with subacute thyroiditis showed a sensitivity of 72.4%, specificity of 89.0%, positive predictive value of 80.4%, and negative predictive value of 83.8%. Twenty-two patients (3.1%) had concomitant papillary thyroid carcinoma, 10 of whom underwent thyroidectomy while the remaining 12 opted for active surveillance owing to having low-risk microcarcinomas. Approximately 30% of papillary carcinomas (7/22) were identified during follow-up ultrasonography, but not during the initial scan. All tumors in this false-negative group were latently localized in the bilateral hypoechoic regions of the thyroid and showed no calcified components. Of the 15 tumors that were detected during both initial and follow-up examinations, 7 exhibited calcified components and 5 were located in unaffected areas apart from the inflammatory hypoechoic region. Subacute thyroiditis highly obscures any coexisting papillary carcinoma when inflammatory hypoechoic regions are present. Ultrasonographic re-examination after a sufficient interval is indispensable for patients with subacute thyroiditis.

Key words: Subacute thyroiditis, Thyroid nodule, Papillary thyroid carcinoma, Hypoechoic area, Calcification
inflammatory disease, approximately 70% of patients stop undergoing medical follow-ups within 6 months after the diagnosis of their condition [4]. Therefore, very few patients undergo ultrasonographic re-examination if no nodules are found at the initial examination. We previously reported that 2 of 5 patients with subacute thyroiditis who had concurrent papillary carcinoma did not have their malignancies detected at the time of their initial ultrasonographic examination but during follow-up 3–6 months later when the inflammatory hypoechoic regions disappeared [16]. Consequently, we began to routinely perform ultrasonographic re-examination of patients with subacute thyroiditis during their follow-up visits after their inflammatory hypoechoic regions disappeared, regardless of the presence or absence of nodular lesions at their initial examination.

In this study, we performed a longitudinal evaluation of patients with subacute thyroiditis to investigate the diagnostic accuracy of ultrasonography in terms of identifying nodular lesions and detecting thyroid carcinoma.

**Patients and Methods**

**Patients**

We investigated 710 untreated patients (610 women and 100 men) with subacute thyroiditis (mean age ± standard deviation, 50.6 ± 11.6 years) who visited Kuma Hospital between 2008 and 2018. Early-phase subacute thyroiditis was diagnosed according to the guidelines of the Japan Thyroid Association [17]; these included painful swelling and tenderness in the thyroid gland, elevated C-reactive protein and serum free thyroxine, decreased levels of serum thyroid stimulating hormone, and a hypoechoic region at the thyroid site of pain as confirmed by ultrasonography. Patients with painful Hashimoto’s thyroiditis were excluded per previously described criteria [18, 19]. This study was approved by the Ethics Committee of Kuma Hospital. Informed consent was obtained from each patient prior to the initiation of this study.

Patients diagnosed with subacute thyroiditis were either treated with prednisolone (n = 572) or non-steroidal anti-inflammatory drugs (n = 48), or were not treated at all (n = 90). All patients underwent ultrasonographic examination at the onset of their symptoms and again within 1 year following the disappearance of the inflammatory hypoechoic regions. The mean follow-up period was 143.4 ± 61.8 days from initial examination. If a nodular lesion was detected at follow-up, its persistence was confirmed using additional ultrasonographic re-examination several months later (Fig. 1).

**Ultrasonography and fine needle aspiration biopsy**

The APLIO 80 SSA-770A (Toshiba Medical Systems Co., Ltd., Otawara, Japan) or APLIO 500 TUS-A500 (Toshiba) instrument with PLT-805AT (Toshiba) or PLT-1005BT (Toshiba) probes were used for ultrasonography, which was performed by well-trained registered medical sonographers as reported previously [16]. The hypoechoic area was defined as an echo density that was clearly lower than that in normal subjects.
Nodular lesions were classified into 3 categories based on ultrasonographic findings: cystic (mixed) nodules, purely solid nodules, and nodules with calcification. In patients with multiple types of nodules, those with the highest malignant potential on ultrasonography were prioritized [5, 20]; the largest nodule was prioritized when nodules were of equal malignant potential. Additionally, fine needle aspiration cytology was performed for nodular lesions that were ‘suspicious for malignancy’ on ultrasonography and/or for solid nodules larger than 1 cm at the largest diameter (Fig. 1) [5, 20].

Statistical analysis

Comparisons of 2 groups were performed using the $\chi^2$ test. Differences in tumor sizes were evaluated using the univariate Mann–Whitney $U$ test. Differences were considered significant at $p < 0.05$.

Results

Frequency of thyroid nodules at initial diagnosis and follow-up

Inflammatory hypoechoic regions were detected in the unilateral and bilateral lobes in 160 and 550 patients, respectively. Ultrasonographic examination revealed thyroid nodules in 245 patients at their initial screening and in 272 patients at their second screening (at follow-up). The first screenings included 75 false-negative results where nodules were eventually identified at the time of the second screening, as well as 48 false-positive results in which inflammatory regions were initially mistaken for nodules (Table 1). The sensitivity of ultrasonography for detecting thyroid nodules at the initial screening was 72.4%; moreover, the specificity, positive predictive value, and negative predictive value were 89.0%, 80.4%, and 83.8% respectively.

Sequential ultrasonographic findings in 22 patients with papillary carcinoma

Ultrasound-guided fine needle aspiration biopsy revealed that 22 nodules were malignant; i.e., a prevalence of 3.1% among 710 patients with subacute thyroiditis (Fig. 1 and Table 1). All malignant tumors were papillary carcinomas with cytological findings of intranuclear inclusions or grooves. The proportion of malignancies in the false-negative group (Table 2, patients 1–7) was similar to that in the true-positive group (Table 2, patients 8–22; $p = 0.67$). Their clinical and ultrasonographic findings of all 22 patients with papillary carcinomas are shown in Table 2. All patients were women and papillary carcinoma tumor sizes varied from 4 to 51 mm in maximum diameter. The tumor sizes in the false-negative group were significantly smaller than those in the true-positive group (median, 5 vs. 8 mm; $p = 0.035$). Ten patients underwent thyroidectomy, after which papillary thyroid carcinoma was pathologically confirmed; the remaining 12 patients underwent active surveillance for their low-risk microcarcinomas (Table 2). In the true-positive group, 7 tumors had calcified components (Fig. 2, patient 10) while the remaining 5 were located at the unaffected area apart from the inflammatory hypoechoic region. In contrast, all tumors in the false-positive group were located within the inflammatory hypoechoic regions and showed no calcification (Fig. 2, patients 1 and 6).

Discussion

The prevalence of thyroid carcinoma among patients with subacute thyroiditis has been unclear; this may be
attributable to the inaccurate diagnoses of nodular lesions at initial ultrasonographic examinations as well as a high proportion of patients lost to follow-up owing to the self-limiting nature of their disease. In our longitudinal evaluation of 710 patients with subacute thyroiditis, we found that 22 of them had concomitant papillary carcinoma; *i.e.*, a prevalence of 3.1%. Similarly, Takebe et al. had previously reported a thyroid carcinoma prevalence rate of 3.5% after performing thyroidal mass screening of 1,048 healthy women aged 30 years or older in Japan using ultrasonography and fine needle aspiration cytology [21]. Both subacute thyroiditis and papillary carcinoma occur most frequently in middle-aged women (40–50 years) [1, 10, 22]. These findings suggest that the frequency of papillary carcinoma among patients with subacute thyroiditis is similar to that among the healthy population. Importantly, approximately 30% of patients with papillary carcinomas (7/22) were in the false-negative group and the frequencies of this disease were similar to the true-positive group (Table 2), suggesting that initial ultrasonographic examination is inadequate for detecting latent thyroid carcinoma in patients with subacute thyroiditis.

In this study, all patients who belonged to the false-negative or false-positive groups showed no calcified components on ultrasonographic examination (Table 1). In contrast, calcification was persistently detected in 14 nodules in the true-positive group and half of them [7] were malignant (Tables 1 and 2). Calcification is frequently observed on ultrasonography in patients with papillary thyroid carcinoma; a recent study found that 725 of 941 patients with papillary carcinoma (77%) had some calcification (punctate microcalcification, speckled calcification, fragmentary calcification, massive calcification, and/or egg-shell calcification) on ultrasonography [23]. Previously, we reported that calcification adjacent to hypoechoic regions in the thyroid may be evidence of malignancy, as was the case for 5 of our patients with

| Table 2 Sequential changes of ultrasonographic findings in 22 patients with papillary thyroid carcinoma |
|-----------------------------------------------|---------------|----------------|--------------|----------------|---------------|
| Pt | Sex | Age | Medication | Follow-up interval (days) | Hypoechoic area | Tumor content | Tumor location | Tumor size (mm) | Surgery |
|----|-----|-----|------------|---------------------------|----------------|--------------|----------------|----------------|---------|
| 1  | F   | 63  | PSL        | 133                       | B             | —            | L             | 8              | + (near trachea) |
| 2  | F   | 57  | None       | 226                       | B             | —            | R             | 4              | —       |
| 3  | F   | 63  | NSAID      | 154                       | B             | —            | I             | 5              | —       |
| 4  | F   | 67  | PSL        | 100                       | B             | —            | L             | 5              | —       |
| 5  | F   | 38  | PSL        | 77                        | B             | —            | L             | 5              | —       |
| 6  | F   | 44  | PSL        | 134                       | B             | —            | R             | 12             | +       |
| 7  | F   | 60  | PSL        | 126                       | B             | —            | I             | 7              | —       |
| 8  | F   | 48  | PSL        | 99                        | R             | Calc         | L             | 7              | —       |
| 9  | F   | 54  | PSL        | 91                        | B             | Calc         | L             | 10             | 9       |
| 10 | F   | 48  | None       | 128                       | B             | Calc         | L             | 10             | 15      |
| 11 | F   | 60  | None       | 107                       | R             | Calc         | L             | 7              | 8       |
| 12 | F   | 53  | None       | 90                        | B             | Calc         | R             | 8              | 8       |
| 13 | F   | 45  | PSL        | 98                        | B             | Calc         | L             | 6              | 13      |
| 14 | F   | 48  | PSL        | 141                       | B             | Calc         | L             | 10             | —       |
| 15 | F   | 71  | PSL        | 96                        | L             | Solid        | R             | 13             | 12      |
| 16 | F   | 48  | PSL        | 224                       | L             | Solid        | I             | 5              | 6       |
| 17 | F   | 75  | None       | 153                       | B             | Solid        | I             | 8              | 8       |
| 18 | F   | 50  | None       | 88                        | L             | Solid        | R             | 16             | 17      |
| 19 | F   | 64  | PSL        | 169                       | B             | Solid        | R             | 9              | 4       |
| 20 | F   | 48  | None       | 113                       | R             | Solid        | L             | 49             | 51      |
| 21 | F   | 77  | PSL        | 168                       | R             | Solid        | L             | 9              | 10      |
| 22 | F   | 65  | PSL        | 135                       | B             | Solid        | R             | 6              | 7       |

F, female; PSL, prednisolone; NSAID, non-steroidal anti-inflammatory drug; B, bilateral lobes; R, right lobe; L, left lobe; I, isthmus; LN meta, lymph node metastasis
In our current large-scale study, we observed a high malignancy rate in nodules with calcified components among patients with subacute thyroiditis. In addition, all 7 carcinomas in the false-negative group were latently localized in the bilateral hypoechoic regions of the thyroid at the first ultrasonography (Table 1). In other words, it was difficult to identify latent papillary carcinoma in bilateral hypoechoic regions that did not exhibit calcification on the initial ultrasonographic examination.

In this study, 1.4% of the patients with subacute thyroiditis underwent surgery for thyroid carcinoma, while 1.7% opted for active surveillance given that they had microcarcinomas ≤10 mm without other risk factors. Active surveillance is highly recommended as the first-line management for low-risk microcarcinomas [24]. Although the incidence rate of thyroid carcinoma has rapidly increased in the United States and Korea, mortality rates owing to this disease remain stable [25, 26]. The increased incidence rate not reflected by higher mortality is mostly due to improved microcarcinoma detection [25, 26]. While the majority of tumor sizes were estimated to be approximately 1 cm in diameter at initial detection (Table 2), it is difficult to determine the precise sizes or localizations of these tumors in the presence of inflammatory hypoechoic regions. Therefore, it is critical to re-evaluate the thyroid after these inflammatory reactions have resolved in order to determine the most appropriate management strategy for any papillary carcinoma that is present (surgery or active surveillance).

In conclusion, we found that subacute thyroiditis can highly obscure any coexisting papillary thyroid carcinoma when inflammatory hypoechoic lesions are present. To avoid missing concomitant thyroid carcinomas, ultrasonographic re-examination after a sufficient interval is indispensable for patients with subacute thyroiditis.

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Author Disclosure Statement

None of the authors have any potential conflicts of interest associated with this research.
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