Longitudinal changes in an autonomously functioning thyroid nodule with coexisting follicular thyroid carcinoma over 14 years

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Abstract

We present a female patient with autonomously functioning thyroid nodule (AFTN) and coexisting follicular thyroid carcinoma (FTC). At age 21, a left thyroid nodule was incidentally detected on computer tomography (CT) scan. At age 33, she had cervical compression and CT showed the left thyroid nodule had increased in size from 13 to 27 mm. Laboratory investigation showed subclinical hyperthyroidism with positive for anti-thyroid peroxidase antibody and normal level of serum thyroglobulin. Repeated fine needle aspiration cytology diagnosed with follicular neoplasm with Hashimoto’s thyroiditis. At age 35, she presented with palpitations due to overt hyperthyroidism. The left thyroid nodule increased in diameter to 33 mm, and thyroid scintigraphy showed elevated uptake in the left thyroid nodule, indicating an AFTN. Thyroidectomy was performed, and the left thyroid nodule was pathologically diagnosed with FTC with capsular invasion. In this case, the longitudinal increase in AFTN size suggested FTC and led to thyroidectomy.

INTRODUCTION

Autonomously functioning thyroid nodule (AFTN) accounts for 0.3% of hyperthyroidism cases, and it comprises 0.5–0.8% of all thyroid nodules [1]. Amelioration of hyperthyroidism in patients with AFTN is achieved by thyroidectomy, anti-thyroid drugs, radioactive iodide (RAI), percutaneous ethanol injection therapy or radiofrequency ablation. Thyroidectomy for AFTN is recommended when thyroid cancer is suspected [2]. However, AFTN with thyroid cancer is rare [3], and such cases are difficult to diagnose pre-operatively.

Here, we report a case of AFTN with coexisting follicular thyroid carcinoma (FTC) in which we were able to follow longitudinal changes in thyroid function and tumor growth over 14 years.

CASE REPORT

A 21-year-old woman underwent right parotidectomy for pleomorphic adenoma. Subsequent cervical computer tomography (CT) incidentally detected a left thyroid nodule (13 mm; Fig. 1A). At age 33, she felt discomfort in the left anterior neck, and cervical CT showed that the left thyroid nodule had increased in diameter to 27 mm (Fig. 1B). Laboratory investigation showed subclinical hyperthyroidism as well as anti-thyroglobulin and anti-thyroid peroxidase antibody positivity. Repeated fine needle aspiration cytology (FNAC) of the left thyroid nodule revealed enlarged follicular cells with uniform nuclear chromatin distribution and lymphocytic infiltration (Bethesda staging: Follicular Neoplasm/Suspicious for Malignancy). The patient was diagnosed with follicular neoplasm, and subclinical hyperthyroidism was considered to be the result of painless thyroiditis due to Hashimoto’s thyroiditis. At age 35, she was referred to our hospital because of a 6-month history of palpitations. On examination, her height was 167 cm and her body mass index was 17.1 kg/m². Her body temperature was 36.5°C, blood pressure was 129/89 mmHg, and heart rate was 96 beats per minute. She exhibited a fine tremor of the hands and a palpable left thyroid nodule without tenderness. She had neither ophthalmopathy nor pretibial myxedema. Laboratory data showed overt hyperthyroidism and negative thyroid-stimulating hormone receptor antibody and thyroid-stimulating antibody, and normal thyroglobulin range (SRL Inc., Tokyo, Japan;
Figure 1. Clinical course of an AFTN with coexisting FTC. The gray area indicates the reference ranges of FT4 (open circles, 0.70–1.48 ng/dl), FT3 (open triangles, 1.68–3.67 pg/ml) and TSH (closed circles, 0.35–4.94 μU/ml). Cervical computed tomography shows the AFTN with coexisting FTC (arrowheads) at (A) 14 years before surgery, (B) 2 years before surgery and (C) 1 week before surgery. Arrowheads indicate the thyroid tumor.

Abbreviations: FT4, thyroxine; FT3, triiodothyronine; TSH, thyroid-stimulating hormone.

Table 1. Cervical CT revealed that the thyroid nodule was 33 mm in size (Fig. 1C). Thyroid ultrasonography showed a heterogeneous solid tumor with a smooth border and high vascularity without calcifications (Fig. 2A–C). The tumor size was 28×23×34 mm, and the ACR Thyroid Imaging, Reporting, and Data System score was 3 points, indicating category TR3 [4]. Thyroid scintigraphy using technetium 99m pertechnetate showed elevated uptake in the left thyroid nodule (Fig. 2D), indicating an AFTN. Methimazole successfully treated the patient’s hyperthyroidism. Since the size of AFTN increased from 13 to 33 mm over 14 years, we suspected coexisting malignancy, and left thyroid lobectomy was performed. Histopathological examination revealed FTC with capsule invasion (Fig. 3A–C) but no vascular invasion (Fig. 3D). 18F-fluorodeoxyglucose positron emission tomography-CT showed no distant metastasis. The patient was diagnosed with minimally invasive FTC (pT3a [5.0×4.0 cm] pN0cM0, Stage I). No transient postoperative hypothyroidism occurred. Two years postoperatively, the patient was euthyroid and there was no tumor recurrence.

DISCUSSION

We report a case of AFTN with coexisting FTC. Thyroid scintigraphy using technetium 99m pertechnetate led to the diagnosis of AFTN, and lobectomy revealed FTC. Due to cytological findings and the presence of Hashimoto’s thyroiditis at age 21, the patient was initially diagnosed with follicular neoplasm and subclinical hyperthyroidism secondary to painless thyroiditis. Suppression of serum TSH is common in AFTN, but the diagnostic value of TSH is not high [5]. As destructive thyroiditis is generally followed by Hashimoto’s thyroiditis, the finding of TSH suppression in this case was initially thought to be due to Hashimoto’s thyroiditis. Thyroid ultrasonography is also not useful for diagnosing AFTN because there are no specific ultrasonographic features of nodular lesions or blood flow [5]. Thyroid scintigraphy remains the gold standard for AFTN diagnosis [6]. Although 99mTc-pertechnetate is commonly used because iodine restriction is not required, the results should be carefully evaluated because false positives were seen in 5% of patients with non-functioning thyroid nodules [7].
Table 1. Laboratory data on admission

| Laboratory test                  | Values | Reference range |
|---------------------------------|--------|-----------------|
| **Peripheral blood**            |        |                 |
| Leukocytes (×10^3/μl)           | 5.7    | 3.3–8.6         |
| Erythrocytes (×10^8/μl)         | 484    | 435–555         |
| Hemoglobin (g/dl)               | 13.7   | 13.7–16.8       |
| Platelets (×10^4/μl)            | 22.7   | 15.8–34.8       |
| **Serum**                       |        |                 |
| Albumin (g/dl)                  | 4.62   | 4.1–5.1         |
| Total bilirubin (mg/dl)         | 0.7    | 0.4–1.5         |
| Aspartate transaminase (U/l)    | 15     | 13–30           |
| Alanine aminotransferase (U/l)  | 15     | 10–42           |
| Lactate dehydrogenase (U/l)     | 177    | 124–222         |
| Alkaline phosphatase (U/l)      | 108    | 103–322         |
| CRP (mg/dl)                     | 0.02   | < 0.14          |
| Free T3 (pg/ml)                 | 4.81   | 1.68–3.67       |
| Free T4 (ng/dl)                 | 1.61   | 0.70–1.48       |
| TSH (μIU/ml)                    | < 0.01 | 0.35–4.94       |
| Anti-TgAb (IU/ml)               | 536    | 14.1–40.6       |
| Anti-TPOAb (IU/ml)              | 20.7   | 1.1–5.2         |
| TRAb (%)                        | 0.7    | < 15            |
| TSAb (%)                        | 116    | < 120           |
| Thyroglobulin (ng/ml)           | 3.96   | < 33.7          |

Abbreviations: Anti-TgAb, anti-thyroglobulin antibody; Anti-TPOAb, anti-thyroid peroxidase antibody; CRP, C-reactive protein; T3, triiodothyronine; T4, thyroxine; TSH, thyroid-stimulating hormone; TRAb, thyroid-stimulating hormone receptor antibody; TSAb, thyroid-stimulating antibody.

AFTN is generally associated with benign tumors, and the prevalence of AFTN with malignancy in patients undergoing resection of solitary, hyperfunctioning thyroid nodules was 3.1% [8]. Regarding the histological subtypes of thyroid carcinoma with AFTN, the incidences of FTC and papillary thyroid carcinoma (PTC) were 46.5 and 46.7%, respectively [8]. PTC is much more prevalent than FTC among thyroid carcinomas without AFTN, and therefore the prevalence of FTC is higher among those with AFTN [8]. The presence of rapid tumor growth, tumor size over 30 mm, elevated serum thyroglobulin concentration or symptoms of neck compression in AFTN are suggestive of malignancy [9]. Longitudinal observation of benign AFTN demonstrated that tumor growth and thyrotoxicosis exacerbation were both rare (4.8 and 6.4%, respectively) [9]. Ultrasonographic features of large size, low echogenicity or microcalcification might be useful to identify malignant AFTN [8]. However, diagnosis remains difficult because ultrasound may show indeterminate features of FTC in malignant AFTN [10]. Thyroid scintigraphy is unable to distinguish malignant and benign AFTN because they share common radiological characteristics [8]. In general, higher thyroglobulin levels are observed in malignant AFTN, but the serum thyroglobulin concentration was low in our case. The presence of anti-thyroglobulin antibody due to Hashimoto’s thyroiditis might mask the elevation of thyroglobulin. Thyroid FNAC was previously shown to be ineffective for diagnosing malignant AFTN with FTC because of limitations in identifying FTC [8].

Thyroidectomy is recommended in AFTN patients with cervical compression or those in whom there is a concern regarding coexisting thyroid cancer [2]. RAI was utilized in patients with a previous neck operation, small tumor size or those in whom surgery is anticipated to be difficult [3]. RAI therapy was found to result in insufficient tumor shrinkage and improvement of cervical compression in AFTN patients with thyroid cancer [8]. In our patient, longitudinal growth of the thyroid tumor caused us to suspect thyroid cancer, and thyroidectomy was performed. No recurrence of FTC was detected 2 years after surgery.

In conclusion, we observed longitudinal changes in AFTN with FTC over 14 years. Surgical treatment of AFTN is recommended when tumor growth is confirmed.

**CONFLICT OF INTEREST STATEMENT**

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Figure 2. Images of AFTN with coexisting FTC. (A) Long-axis view, (B) short-axis view and (C) preoperative color Doppler thyroid ultrasonography. (D) Increased uptake of technetium 99m pertechnetate in thyroid scintigraphy (arrow).

Figure 3. Histopathology of FTC. (A) Hematoxylin and eosin (HE) staining of FTC. Scale bar = 5 mm. (B) High magnification of FTC (HE staining). Scale bar = 100 μm. (C) Capsular invasion of FTC (arrowheads) under Elastica van Gieson staining. Scale bar = 500 μm. (D) No vascular invasion of FTC (arrows) under Azan staining. Scale bar = 200 μm. Abbreviations: FTC, follicular thyroid carcinoma.
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ETHICAL APPROVAL
Not required.

PATIENT CONSENT
Written informed consent was obtained from the patient.

GUARANTOR
Hideki Yamaguchi.

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