Evaluation of Hot Nodules of Thyroid Gland Using Tc-99m Pertechnetate: a Novel Approach Using Quantitative Single-Photon Emission Computed Tomography/Computed Tomography

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Abstract

Planar scintigraphy using Tc-99m pertechnetate is useful for snapshot evaluation of hot thyroid nodules, which are pathologically follicular adenoma and seldom, if ever, malignant. The autonomy of the hot nodules has been demonstrated by the presence of thyroid-stimulating hormone-dependent extra-nodular thyroid tissue besides the hot nodules. Here, we present two cases of hot thyroid nodules in patients who underwent quantitative single-photon emission computed tomography/computed tomography (SPECT/CT). In addition to the nodules, contralateral normal thyroid parenchyma was evaluated based on standardized uptake values. One patient had a traditional follicular adenoma suppressing other thyroid tissue, whereas the other patient seemed to have a nodule erupting from underlying hyperfunctioning, not suppressed, thyroid tissue. This novel approach using quantitative SPECT/CT unveils a new pathology of hot thyroid nodule that does not suppress, but coincides with hyperfunctioning thyroid tissue.

Keywords Thyroid · Hot nodule · Quantitation · Single-photon emission computed tomography · Computed tomography · Tc-99m pertechnetate · Standardized uptake value

Introduction

The role of radionuclide scan for the evaluation of thyroid nodules is reported to be limited because fine needle aspiration biopsy (FNAB) and ultrasonography (US) play major roles in the differential diagnosis of thyroid nodules [1, 2]. However, the functional status of thyroid nodules is of paramount importance, especially for treatment planning. Hot uptake of radionuclides in thyroid nodules with or without suppressed uptake in other thyroid tissue can lead to the decision to administer radioactive iodine (RAI) treatment, of which the cure

rate is reported to be as high as 75–90% with rare side effects, such as hypothyroidism [3, 4]. When FNAB results are indeterminate, radionuclide scan is helpful for treatment decisions; if hot uptake is detected in the thyroid nodule of interest, surgery for pathologic confirmation of the indeterminate nodule might be excluded because the malignant potential of the functioning nodule will be very low [5, 6].

In radionuclide scans, radio-iodine or Tc-99m pertechnetate has been used; radio-iodine is preferred to Tc-99m pertechnetate [1, 2] because Tc-99m pertechnetate is not retained in thyroid tissue for more than 1 h [7]. However, Tc-99m pertechnetate holds promise as a thyroid imaging agent due to its hands-on availability, excellent image quality, and low radiation exposure [8]. Furthermore, within 30-min post-injection, thyroid retention of Tc-99m pertechnetate is stable [9, 10]. Thus, Tc-99m pertechnetate thyroid scintigraphy has been successfully performed when the scans were acquired around 20-min post-injection [11, 12]. Regarding quantitative gamma camera imaging, Tc-99m pertechnetate has advantages over radio-iodine, because correction algorithms for attenuation, scatter, and collimator–detector response have been established for Tc-99m pertechnetate [13, 14], but not for radio-iodine. Recently, Tc-99m pertechnetate quantitative

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single-photon emission computed tomography/computed tomography (SPECT/CT) has been successfully applied in a variety of functional thyroid diseases [15–17].

Functioning thyroid nodules are traditionally referred to as autonomously functioning thyroid nodules (AFTNs). AFTNs are defined by the presence of thyroid-stimulating hormone (TSH)-independent (that is, autonomous) thyroid nodules and extra-nodular thyroid tissue that is dependent on TSH for the functional status. The autonomy of thyroid nodules has been investigated using thyrotropin-releasing hormone (TRH) stimulation or triiodothyronine (T3) suppression tests. Both tests are performed to demonstrate the presence of extra-nodular thyroid tissue that is dependent on TSH, while the hot nodule is not influenced by changes in TSH. For extra-nodular thyroid tissue, increased Tc-99m pertechnetate uptake after TRH-induced TSH elevation or decreased Tc-99m pertechnetate uptake after T3-induced TSH suppression is the indicator of TSH-dependent extra-nodular thyroid tissue. However, in the era of US and highly sensitive TSH, without those tricky provocation tests for the presence of TSH-dependent extra-nodular thyroid tissue, it is easy to determine the functional status of thyroid nodules. That is, thyroid nodules with high uptake of Tc-99m pertechnetate in conjunction with low TSH levels are considered to be compatible with traditional AFTNs [2]. No further attention is being paid to the functional status of extra-nodular thyroid tissue.

In the current two case reports, we describe different characteristics of extra-nodular thyroid tissue amid the same conditions of hot nodules with low TSH levels. Using the quantitative parameter of standardized uptake value (SUV) derived from Tc-99m pertechnetate SPECT/CT, the functional statuses of hot thyroid nodules as well as extra-nodular thyroid tissue were investigated. Functioning thyroid nodules may suppress other thyroid tissues, which is the conventional concept of AFTNs. However, functioning thyroid nodules may erupt from the pre-existing condition of hyperfunctioning thyroid disease.

Case Report

Case 1

A 54-year-old woman presented with thyroid function test (TFT) abnormality. She complained of mild fatigue and had lost 15 kg of her weight in the past 1 year. She did not have any underlying disease, but a nodule was present in her left thyroid lobe, which had been diagnosed as benign 1 year ago. Her serum TSH level was significantly low (<0.05 $\mu\text{IU/mL}$, normal reference range of 0.3 – 4.0 $\mu\text{IU/mL}$), while free T4 (1.59 ng/dL , normal reference range of 0.89 – 1.79 ng/dL) and T3 (173 ng/dL , normal reference range of 79 – 200 ng/dL) levels were within normal ranges, indicating subclinical

hyperthyroidism. The nodule size was increased from $2.3 \times 1.6 \times 1.2$ cm in 2005 to $3.0 \times 1.7 \times 4.7$ cm in 2016 (Fig. 1a). FNAB for the nodule was performed again, and histopathologic examination showed a benign follicular adenoma (Fig. 1b). Because the free T4 level was elevated to 1.96 ng/dL 3 months later, the patient was administered beta-blockers, and she underwent quantitative Tc-99m pertechnetate SPECT/CT for functional evaluation of the nodule. The detailed protocol of the quantitative SPECT/CT acquisition is available in the literature [15–17]. The planar anterior scintigraphy image and SPECT/CT showed a nodular lesion with increased Tc-99m pertechnetate uptake in the left thyroid lobe (maximum counts on planar image, 234), whereas the remaining thyroid tissue showed faint or little uptake (maximum counts on planar image, 31) (Fig. 1c, d). The quantitative analysis revealed the %thyroid uptake for both thyroid lobes as 2.31% , which was higher than the reported normal range in euthyroid patients ($0.78 \pm 0.50\%$, $n = 20$), but within the reported range in patients with Graves' disease ($5.28 \pm 5.19\%$, $n = 17$), with each reference range having been determined using the same SPECT/CT protocol [15, 17] (Fig. 3a). The maximum SUV (SUVmax) of the left thyroid nodule was 153.91 , which fell into the Graves' disease range (196.62 ± 118.47 , $n = 17$) and was above the euthyroid range (45.56 ± 30.74 , $n = 20$) [15, 17]. However, the SUVmax of the contralateral right thyroid parenchyma was only 4.96 , which was significantly lower, even compared with the euthyroid range (Fig. 3b), indicating functionally suppressed extra-nodular thyroid tissue. Anti-TSH receptor antibodies were not detected in this patient (<0.3 IU/L, normal reference range of 0.3 – 1.22 IU/L). She was administered I-131 (555 MBq) 6 months later, and remained in a clinically and biochemically euthyroid state until 1 year later when the last follow-up information was available.

Case 2

A 51-year-old woman who harbored a nodule in the right thyroid lobe visited our clinic. She complained of sweating and weight loss of 5 kg in the past 2 months. Her vital signs were all normal, and the physical examination was unremarkable except for an enlarged, painless right thyroid lobe. Her TFT tests exhibited overt hyperthyroidism (TSH, <0.05 $\mu\text{IU/mL}$; free T4, 2.37 ng/dL ; and T3, 206 ng/dL). Thyroid US showed an indeterminate nodule with a size of $2.1 \times 1.59 \times 2.3$ cm in the right thyroid lobe (Fig. 2a). FNAB of the right thyroid nodule was performed, and histopathologic examination revealed a follicular proliferative lesion favoring benign characteristics. Interestingly, some lymphoplasmacytic infiltration was noted (Fig. 2b), which was not observed in case 1 (Fig. 1b). Quantitative SPECT/CT using Tc-99m pertechnetate was also performed for this patient. A hot nodule was observed in the right middle lobe (maximum counts on planar image, 644), and the contralateral left thyroid

Fig. 1 Autonomously functioning thyroid nodule. **a** A thyroid nodule is observed in the left lobe on thyroid ultrasonography. **b** Histologic finding of the thyroid nodule. Variable-sized follicles are shown, which indicate a benign follicular lesion. **c** The planar anterior image of Tc-99m pertechnetate thyroid scintigraphy and **d** SPECT/CT showed a nodular lesion with increased uptake in the left thyroid lobe, whereas the remaining thyroid tissue showed faint uptake

parenchyma appeared to be relatively suppressed in planar scintigraphy and SPECT/CT images (maximum counts on planar image, 408) (Fig. 2c, d). The %thyroid uptake for both thyroid lobes increased to 3.22% (Fig. 3a). However, the SUVmax differed from that in case 1. The SUVmax of the right thyroid nodule was in the Graves' disease range as

203.35. Interestingly, the SUVmax of contralateral thyroid tissue (153.07) was also substantially greater than the euthyroid range and was almost equivalent to the SUVmax of AFTN (153.91) in case 1 (Fig. 3b). This patient had an increased anti-TSH receptor antibody (3.34 IU/L) level, suggesting the presence of underlying autoimmune disease.

Fig. 3 Quantitative parameters for cases 1 and 2 with reference to Graves' disease and euthyroid patients [15, 17]. **a** %thyroid uptake for both thyroid lobes. **b** SUVmax for the hot thyroid nodules and contralateral extra-nodular thyroid tissue

Fig. 2 Functioning hot thyroid nodule in the background of hyperfunctioning thyroid disease. **a** Thyroid ultrasonography showed a thyroid nodule in the right lobe. **b** Histologic finding of the thyroid nodule. There are variable-sized benign-looking follicles. Additionally, lymphoplasmacytic infiltration was observed (arrow). **c** The planar anterior image of Tc-99m pertechnetate thyroid scintigraphy and **d** SPECT/CT revealed a hot nodule in the right middle lobe, and the contralateral left thyroid parenchyma appeared to be relatively suppressed

I-131 therapy was not considered for this patient, but instead, anti-thyroid medication (methimazole) was prescribed for 18 months. She was maintained in the euthyroid state until a recent follow-up 18 months after discontinuing methimazole administration.

Discussion

The natural course of conventional AFTNs is known to be benign. Literally, the malignant potential of AFTNs is very low. In terms of progression to overt hyperthyroidism, typical AFTNs remain in the euthyroid state for a long time, and observation and clinical follow-ups are sufficient in many clinical situations (nontoxic AFTNs) [18]. When hot nodules result in clinical hyperthyroidism, they are referred to as toxic AFTNs, toxic adenoma, or toxic nodular goiter. Toxic nodular goiters are the second most common cause of hyperthyroidism following Graves' disease and are believed to progress to toxic multi-nodular goiters as Plummer's disease. RAI treatment and surgery are the main treatment options for toxic AFTNs [3, 19]. We believe that case 1 involves typical toxic AFTN that was effectively managed by RAI therapy.

On the other hand, case 2 seems to involve a variant of nodular Graves' disease [20], which is supported by the presence of anti-TSH receptor antibodies and lymphoplasmacytic infiltration (Fig. 2b), which are reminiscent of autoimmune thyroid disease [21]. Furthermore, favorable response to anti-thyroid drugs in case 2 is another indirect evidence of

underlying Graves' disease. If high-dose RAI was administered in case 2, permanent hypothyroidism might be unavoidable because the extra-nodular thyroid tissue would be highly responsive to the RAI as the hot nodule. The high SUVmax of the extra-nodular thyroid tissue (Fig. 3b) may indicate the functional status and thus be able to predict the therapeutic efficacy of RAI administration. The maximum counts value measured from the planar image could not reveal whether the extra-nodular parenchyma uptake is normal, suppressed, or hyperfunctioning state. However, the standardized value, SUV, can be used to determine the thyroidal functional status by comparison with the reference value. The true etiology of case 2 remains elusive, but the functional statuses of the hot nodule and other thyroid tissue were effectively assessed using novel quantitative SPECT/CT.

According to the 2015 guideline of the American Thyroid Association, the foremost test for evaluation of thyroid nodules is a check-up for TSH levels [2]. If TSH levels are suppressed, radionuclide scans are recommended for the evaluation of possible AFTNs. We believe that if the recommended radionuclide scans were quantitative Tc-99m pertechnetate SPECT/CT, as demonstrated in the current case reports, it would be more informative in the clinical practice. The reason is twofold: one is that pathologic tests, such as FNAB, can be omitted, especially for single hot nodules with low TSH levels due to a low incidence of malignancy, like in case 1 [4]; the other is that therapeutic decisions may be affected by the knowledge of the functional status of extra-nodular thyroid tissue, as in case 2 [20].

Conclusion

We report two cases of hot thyroid nodules, the functional states of which were quantitatively evaluated using Tc-99m pertechnetate thyroid SPECT/CT. Quantitative SPECT/CT might be a useful tool for the evaluation of thyroid nodules with low TSH levels.

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Compliance with Ethical Standards

Conflict of Interest Reeree Lee, Young So, Yoo Sung Song, and Won Woo Lee declare that there is no conflict of interest.

Ethical Approval The study was approved by an institutional review board (IRB) and was performed in accordance with the ethical standards set in the 1964 Declaration of Helsinki and its later amendments.

Informed Consent The need for patients' informed consent was waived by the IRB.

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