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Causes of appearance of scintigraphic hot areas on thyroid scintigraphy analyzed with clinical features and comparative ultrasonographic findings

Masahiro IWATA,* Kanji KASAGI,** Hiroto HATABU,*** Takashi MISAKI,****
Yasuhiro IIDA,**** Toru FUJITA**** and Junji KONISHI****

*Department of Radiology, Hikone Municipal Hospital
**Department of Nuclear Medicine, Takamatsu Red Cross Hospital
***Pulmonary Functional Imaging Research, University of Pennsylvania Medical Center
****Department of Nuclear Medicine and Diagnostic Imaging, Kyoto University Graduate School of Medicine

This study was done retrospectively to analyze the ultrasonographic (US) findings in thyroid scintigraphic hot areas (HA). Three-thousand, eight-hundred and thirty-nine consecutive patients who underwent ^{99m}Tc-pertechnetate (n = 3435) or ^{123}I (n = 457) scintigraphy were analyzed. HA were regarded as present when the tracer concentration was greater than the remaining thyroid tissue, or when hemilobar uptake was observed. High-resolution US examinations were performed with a real-time electronic linear scanner with a 7.5 or 10 MHz transducer. One hundred and four (2.7%) were found to be scintigraphic HA (n = 120). US revealed a nodular lesion or well-demarcated thyroid tissue corresponding to the HA in 94 areas (78.4%, Category 1), an ill-defined region with different echogenicity in 13 areas (10.8%, Category 2), and no correlating lesion in 13 areas (10.8%, Category 3). These 104 patients included 43 with adenomatous goiter (59 areas), 33 with adenoma, 11 with Hashimoto's thyroiditis, 5 with primary thyroid cancer, 4 with euthyroid ophthalmic Graves' disease (EOG), 3 with hemilobar atrophy or hypogenesis, 2 with hemilobar agenesis, 2 with hypothyroidism with blocking-type TSH-receptor antibodies (TSHRAb), 1 with acute suppurative thyroiditis. Among the 59 adenomatous nodules and 33 adenomas, 51 (86.4%) and 32 (97.0%), respectively, belonged to Category 1. A solitary toxic nodule was significantly larger and occurs more often in older patients than in younger patients. On the other hand, all 17 patients with known autoimmune thyroid diseases including Hashimoto's thyroiditis, EOG and hypothyroidism with blocking TSHRAb belonged to Category 2 or 3. Possible underlying mechanisms are 1) hyperfunctioning tumors or nodules, 2) localized functioning thyroid tissue freed from autoimmune destruction, inflammation or tumor invasion, 3) congenital abnormality, 4) clusters of hyperactive follicular cells caused by long-term TSH and/or TSHRAb stimulation, 5) asymmetry, etc. Scintigraphic HA are observed in patients with various thyroid diseases and high-resolution US appears to be helpful clinically for the differential diagnosis of the above mentioned disorders.

Key words: thyroid scintigraphy, hot areas, ultrasonography

INTRODUCTION

THYROID SCINTIGRAPHY with ^{99m}Tc or ^{123}I provides regional functional images of the thyroid gland. High-resolution ultrasonography (US), on the other hand, provides morphological information more precisely than thyroid scintigraphy, and is now widely used in patients with various thyroid diseases. Scintigraphic and sonographic correlation studies have revealed that the presence of non-functioning tumors, inflammation, cysts and avascular lesions is responsible for the emergence of cold areas on ^{123}I or ^{99m}Tc scan images.[1,2] Although it is widely

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For reprint contact: Masahiro Iwata, M.D., Department of Radiology, Hikone Municipal Hospital, 2–1–45, Honmachi, Hikone, Shiga 522–8539, JAPAN.
E-mail: Masahiro.Iwata@ma3.seikyou.ne.jp

accepted that scintigraphic hot areas (HA) are mostly due to the presence of a cluster of functioning follicular cells, there have been no reports in which the causes of such scintigraphic features were investigated in a large population of patients. In the present study, through analysis of HA in relation to US findings and clinical features of thyroid diseases, we have found that scintigraphic HA are observed in a variety of patients including those with autonomously functioning thyroid nodule (AFTN). We have also discussed the underlying mechanism in each pathological condition.

MATERIALS AND METHODS

Three thousand, eight hundred and thirty-nine consecutive patients who had underwent thyroid scintigraphy between January 1988 and March 1999 at Kyoto University Hospital formed the study population. The scintigraphic findings were evaluated by 3 experienced radiologists (K.K.; T.M.; Y.I.) without knowledge of the clinical features or the laboratory test results. HA was regarded as present when there was a lesion concentrating radioactive agents to a greater degree than the remaining thyroid tissue or thyroidal hemilobar uptake. These 3,839 patients did not include those who had previously been thyroidectomized. The interval between thyroid scintigraphy and US was less than a week.

Thyroid scintigraphy

^{99m}Tc thyroid scintigraphy was performed 30 minutes after intravenous injection of 148 MBq ^{99m}Tc-pertechnetate in 3,435 patients. The net thyroidal ^{99m}Tc uptake was determined by subtracting the background radioactivity just below the thyroid gland (normal range: 0.4–3.0%). Scan images were acquired with a gamma camera equipped with a low-energy parallel-hole collimator (Gamma View-F RC-IC-1635LF, Hitachi Medical Corporation, Chiba, Japan). Between 1,000 to 2,000 counts/cm^2 were collected with the 140-keV photopeak and 20% window.

In 457 patients, ^{123}I thyroid uptake was determined 3 and 24 hours after oral administrations of 7.4 MBq Na^{123}I (normal range: 7–35% after 24 h), and the 3 hour image was acquired with a low-energy collimator. Both ^{123}I and ^{99m}Tc scans were performed in 53 patients. These included 10 patients in whom the ^{123}I scanning was performed in order to confirm the scintigraphic HA observed on the ^{99m}Tc image.

Ultrasonography

US was performed with a high frequency (7.5 or 10 MHz) electronic real-time scanner with a linear transducer (EUB 555 Hitachi, Tokyo, Japan; RT-2800 and LOGIQ 500 MD Yokogawa, Tokyo, Japan). The sonographic findings were classified into three categories: Category 1: US revealed identification of a nodule or a well-demarcated thyroid tissue corresponding to the scintigraphic HA, Category 2: US revealed the presence of an ill-defined area with different echogenicity, Category 3: US revealed no corresponding lesions.

Thyroid in vitro tests

Serum free T_4 concentrations were determined by radioimmunoassay with commercially available kits (Amerlex MAB, Ortho-Clinical Diagnostics, Tokyo, Japan; normal range 12.6–22.8 nmol/*l*). Serum TSH concentrations were measured by immunoradiometric assay (Riagnost hTSH, CIS Diagnosics, Chiba, Japan; normal range 0.3–3.9 mU/*l*). Antithyroglobulin and antimicrosomal antibody titers were determined by means of commercially available kits (SERODIA-ATG and SERODIA-AMC, Fuji Rebio, Tokyo, Japan). TSH-binding inhibitor immunoglobulins (TBII) were assayed with a commercially available kit (TRAb Cosmic II, RSR Limited, Cardiff, United Kingdom). Thyroid-stimulating antibodies (TSAb) and Thyroid stimulation-blocking antibodies (TSBAb) were assayed by the method developed in our laboratory.[3,4] The clinical states were defined according to the following criteria: hyperthyroidism, high free T_4 and undetectable TSH (< 0.03 mU/*l*) levels; subclinical hyperthyroidism, normal free T_4 and reduced TSH; euthyroidism, normal free T_4 and normal TSH; hypothyroidism, normal or reduced free T_4 and high TSH.

The diagnosis of each thyroid disease

The diagnosis of each thyroid disease was determined cyto- or histopathologically and/or clinically. All 5 thyroid cancers, 7 of 33 adenomas, and 11 of 59 adenomatous nodules were diagnosed by postoperative histological examination. The remaining 26 adenomas were diagnosed based on a solitary nodule on US and benignancy on cytological diagnosis by fine needle aspiration biopsy (FNAB). Twenty-six adenomatous nodules were diagnosed on the basis of US findings, such as multiple nodules, cystic degeneration, and/or coarse calcification in an asymmetrically or symmetrically enlarged diffuse goiter[5,6] as well as the cytological diagnosis. In the remaining 25 adenomatous nodules, the diagnosis was made on the basis of US findings alone. The diagnosis of Hashimoto's thyroiditis was made on the basis of diffuse goiter, detectable antimicrosomal and antithyroglobulin antibodies, and decreased echogenicity on thyroid US. The diagnosis of euthyroid ophthalmic Graves' disease (EOG) was made in euthyroid or subclinically hyperthyroid patients with Graves' ophthalmopathy, who usually had detectable TBII and/or TSAb in serum.[7] Hypothyroid patients with detectable TBII and TSBAb were given a diagnosis of hypothyroidism with blocking-type TSH receptor antibody (TSHRAb).[4]

Statical analysis

Data were analyzed for statistical significance by the Student's t test or χ^2 analysis. A p value of < 0.05 was

considered statistically significant.

RESULTS

Among the 3,839 patients who underwent thyroid scintigraphy, 104 (2.7%; 8 males and 96 females; age 51.6 ± 14.8 yr (mean ± SD); range 9–84 yr) were judged to have HA. They included 87 (2.5%) and 26 (5.7%) patients who underwent ^{99m}Tc and ^{123}I scans, respectively. Among the 53 patients in whom both ^{99m}Tc-pertechnetate and ^{123}I scans were performed, 9 showed HA on both scans, and 2 showed HA on one scan. Namely, one with adenoma had a cold lesion on the ^{99m}Tc image and the other with papillary adenocarcinoma had a cold lesion on the ^{123}I image. These 2 patients were included in the 104 patients with scintigraphic HA. Ninety-four patients had a solitary HA, while 10 had multiple HA, with the total number of HA being 120. Table 1 shows that such areas were observed in patients not only with functioning adenoma or functioning adenomatous nodule, but also with other thyroid diseases such as autoimmune thyroid diseases, congenital thyroid diseases, thyroid malignancy

Table 1 Clinical and/or pathological diagnoses of thyroid diseases with scintigraphic hot areas, the number of patients with each thyroid disease classified according to the presence or absence of correlating US lesions, and possible underlying mechanisms

Disease	Number of patients (lesions; %)				Mechanism
	Total	Category 1	Category 2	Category 3	
Adenomatous goiter	43 (59)	37 (51; 86.4)	3 (5; 8.5)	3 (3; 5.1)	Functioning nodule
Adenoma	33	32 (32; 97.0)	1 (1; 3.0)	0	Functioning adenoma
Hashimoto's thyroiditis	11	0	4 (4; 36.4)	7 (7; 63.6)	Residual thyroid tissue saved from self-immunoreactive destruction
Primary thyroid cancer	5	5 (5; 100.0)	0	0	Functioning carcinoma, or nonfunctioing carcinoma adjacent or embedded in functioing tissue
Euthyroid opthalmic Graves' disease	4	0	3 (3; 75.0)	1 (1; 25.0)	Functioning thyroid cells stimulated by TSHRAb
Hemilobar atrophy or hypogenesis	3	3 (3; 100.0)	0	0	Marked asymmetry
Hemilobar agenesis	2	2 (2; 100.0)	0	0	Hemilobar uptake
Hypothyroidism with blocking-type TSH receptor antibody	2	0	0	2 (2; 100.0)	Functioning thyroid cells stimulated by TSHRAb and TSH
Acute suppurative thyroiditis	1	1 (1; 100.0)	0	0	Contralateral healthy lobe uptake
Total	104 (120)	80 (94; 78.4)	11 (13; 10.8)	13 (13; 10.8)	

Category 1: US revealed identification of a nodule or a well-demarcated thyroid tissue corresponding to the scintigraphic HA, Category 2: US revealed presence of an ill-defined area with different echogenicity, Category 3: US revealed no corresponding lesions.

Table 2 Thyroid status in patients with scintigraphic hot areas

Disease	Number of patients				
	Total	Hyperthyroidism	Subclinical hyperthyroidism	Euthyroidism	Hypothyroidism
Adenomatous goiter	43 (33)*	7 (4)*	9 (6)*	25 (21)*	2 (2)*
Adenoma	33	6	5	22	0
Hashimoto's thyroiditis	11	0	0	5	6
Primary thyroid cancer	5	0	1	4	0
Euthyroid ophthalmic Graves' disease	4	0	1	3	0
Hemilobar atrophy or hypogenesis	3	0	0	0	3
Hemilobar agenesis	2	0	0	2	0
Hypothyroidism with blocking-type TSH-receptor antibody	2	0	0	0	2
Acute suppurative thyroiditis	1	0	0	1	0
Total	104	13	16	62	13

2 hyperthyroid and 2 subclinically hyperthyroid patients with adenoma and 2 hyperthyroid and 2 subclinically hyperthyroid patients with adenomatous goiter underwent thyroid scintigraphy under treatment with antithyroid drugs.
(n)* number of patients with a solitary functioning nodule

Table 3a Comparison of sex, age, US diagnoses, thyroid status and ^{99m}Tc uptake between patients with a solitary thyroid functioning nodule and those with multiple functioning nodules

	Solitary (n = 44)	Multiple (n = 6)	Statistical significance
Sex (male/female)	0/44	0/6	NS
Age (yr)	48.8 ± 15.4	50.7 ± 10.4	NS
Adenoma/Adenomatous goiter	25/19	0/6	$p < 0.01$
Hyper/SH/Eu	6/8/30	3/2/1	$p < 0.05$
^{99m}Tc uptake (%)	1.6 ± 1.4	3.1 ± 2.5	$p < 0.05$

NS: no significant difference. Hyper: hyperthyroidism; SH: subclinical hyperthyroidism; Eu: euthyroidism. There were 66 and 10 patients with solitary and multiple functioning nodules, respectively. Among them, 22 and 4 patients, respectively, were excluded because of detection of antithyroglobulin and/or antimicrosomal antibodies, the condition under antithyroid drug treatment and/or Category 3 appearance. Five patients with thyroid cancer were also excluded.

Table 3b Comparison of sex, age, US diagnoses, thyroid status, sonographic findings and ^{99m}Tc uptake among hyperthyroid, subclinical hyperthyroid and euthyroid patients with a solitary functioning adenoma or adenomatous goiter

	1. Hyperthyroidism n = 6 (13.6%)	2. Subclinical hyperthyroidism n = 8 (18.2%)	3. Euthyroidism n = 30 (68.2%)	Statistical significance
Sex (male/female)	0/6	0/8	0/30	NS
Age (year)	60.0 ± 5.3	52.5 ± 15.7	45.5 ± 15.8	1 vs. 3 $p < 0.05$
Adenoma/Adenomatous goiter	4/2	3/5	18/12	NS
Sonographic findings				
Tumor size (cm)	3.9 ± 1.0	2.4 ± 1.3	2.3 ± 1.0	1 vs. 2 $p < 0.05$, 1 vs. 3 $p < 0.005$
Echo-pattern (solid/dominantly solid/ dominantly cystic)	2/4/0	2/3/3	8/14/8	NS
^{99m}Tc uptake (%)	3.2 ± 1.9	1.4 ± 0.8	1.4 ± 0.8	1 vs. 2 $p < 0.05$, 1 vs. 3 $p < 0.01$

NS: no significant difference

and inflammation, etc.

Scintigraphic and unltrasonographic correlation studies revealed that most of the HA (94/120; 78.4%) belonged to Category 1, with identification of corresponding nodules or well-demarcated thyroid tissues. Among the 59 adenomatous nodules observed in 43 patients, 51 nodules (37 patients) (86.4%), 5 nodules (3 patients) (8.5%) and 3 nodules (3 patients) (5.1%) belonged Category 1, 2 and 3, respectively. All patients with thyroid adenoma except one (32/33; 97.0%) belonged to Category 1. All patients with autoimmune thyroid diseases including Hashimoto's thyroiditis, EOG and hypothyroidism with blocking-type TSHRAb belonged to Category 2 or Category 3. Table 2 demonstrates that the thyroid function in patients with scintigraphic HA is variable, the prevalence of hypothyroidism being 12.5% (13/104).

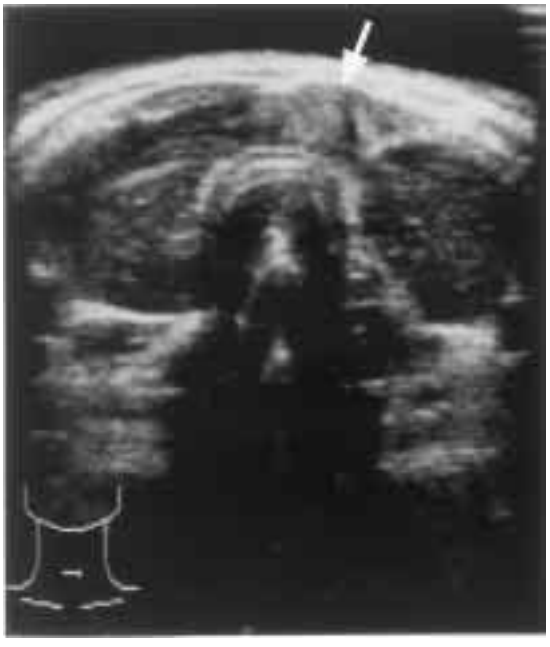
Adenoma and adenomatous goiter

Comparison of sex, age, US diagnoses, thyroid status and ^{99m}Tc uptake in patients with a solitary functioning nodule and those with multiple functioning nodules reveals that the latter was significantly associated with hyperthyroidism ($p < 0.05$, χ^2 analysis) and higher ^{99m}Tc uptake (Table 3a). Comparisons were also made in 44 patients with a solitary functioning nodule, showing different thyroid functions (Table 3b). Hyperthyroid patients were significantly older than euthyroid patients ($p < 0.05$). Of 19 patients older than 50 years and of 25 patients younger than 50 years, 10 (52.6%) and 4 (16.0%), respectively, were overtly or subclinically hyperthyroid ($p < 0.01$, χ^2 analysis). As for the US findings, the hyperthyroid patients had a significantly larger nodule than the subclinically hyperthyroid patients ($p < 0.05$) and euthyroid patients ($p < 0.005$). The echo-pattern (solid or cystic) did not correlate significantly with the thyroid function. ^{99m}Tc uptake was significantly higher in the hyperthyroid patients than in other 2 groups of patients ($p < 0.05$, $p < 0.01$).

Hashimoto's thyroiditis

In this study, 11 patients with Hashimoto's thyroiditis had scintigraphic HA (age 53.6 ± 12.9 yr, range 27–72; 1

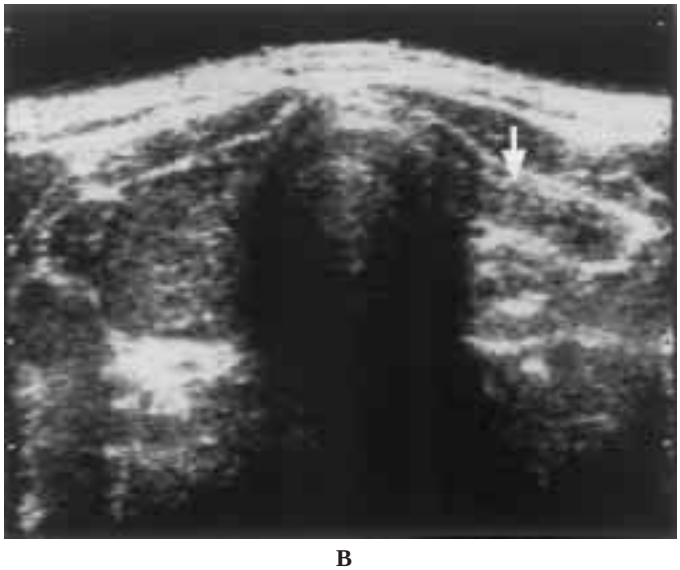
A



B

Fig. 1 A 47-year-old female with Hashimoto's thyroiditis. Slightly increased uptake (*white arrow head*) of radioiodine is observed in the isthmus on ^{123}I scintigram (A). The area is more hyperechoic (*white arrow*) compared with the adjacent tissue that is markedly hypoechoic, but could not be recognized as a nodular lesion (B).

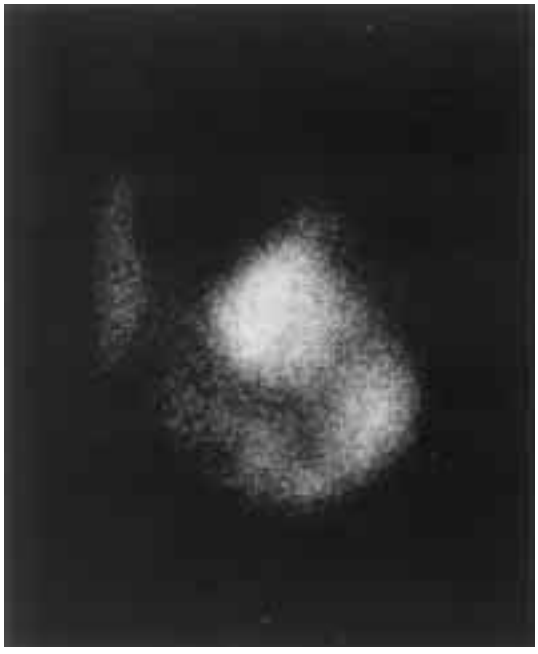
A



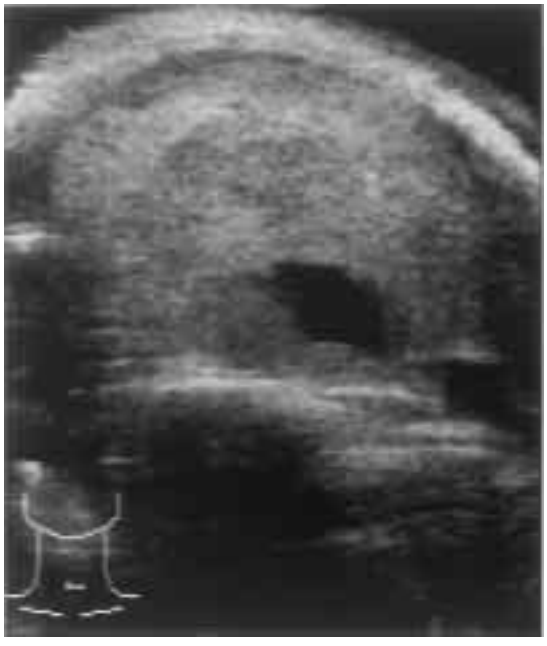
B

Fig. 2 A 47-year-old male with hemilobar atrophy or hypogenesis. Thyroid scintigram shows complete failure of the left lobe to trap ^{99m}Tc-pertechnetate and mild enlargement of the right lobe with homogeneously increased uptake (A). Transverse imaging with US reveals existence of the left lobe (*white arrow*) with severe atrophic change and mild diffuse enlargement of the right lobe. The echogenicity of the whole gland is decreased (B).

male, 10 females). Five were euthyroid, and 6 were hypothyroid. Three euthyroid and 1 hypothyroid patients belonged to Category 2, and 2 euthyroid and 5 hypothyroid patients belonged to Category 3. In Category 2, the correlating area with normal or slightly decreased echogenicity was demarcated from the noticeably hypoechoic remaining thyroid tissue in 3 patients (Fig. 1), or was more hypoechoic than the remaining thyroid tissue in one case. Seven patients in Category 3 all showed diffusely decreased or normal echogenicity. The average ^{99m}Tc uptake at 30 min was $4.1 \pm 6.9\%$ ($n = 9$). ^{123}I uptake values at 24 h were 11.2 and 18.0% in 2 cases. There was no significant correlation between serum TSH concentrations and ^{99m}Tc uptake values (data not shown).

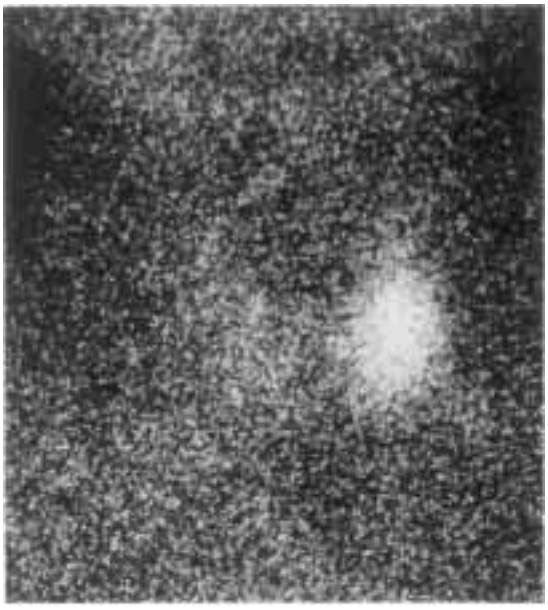


A

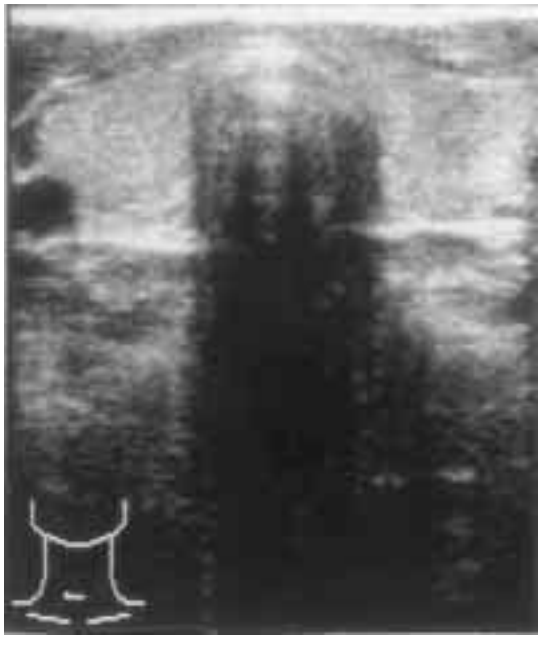


B

Fig. 3 A 59-year-old female with primary thyroid cancer (Papillary adenocarcinoma follicular variant). Hot and cold areas are seen in the left lobe of thyroid gland on ^{99m}Tc scintigram (A). US reveals an isoechoic mass with hypoechoic rim, little cystic change and no calcifications, corresponding to the scintigraphic hot and cold areas. The solid part of the nodule is occupied by the cancer cells on histopathology (B).



A



B

Fig. 4 A 48-year-old male with euthyroid ophthalmic Graves' disease. A scintigraphic hot area is observed in the left lobe. A marked difference in ^{99m}Tc uptake between right and left lobes is observed (A). There is no significant difference in size between left lobe and right lobe. No distinct nodular lesion corresponding to the hot area is seen in the left lobe, although the left lobe appears slightly hypoechoic (B).

Hemilobar atrophy or hypogenesis

In this study, 3 patients (age 49, 66, 75 yr; 2 males and 1 female) with scintigraphic unilateral uptake were proved to have severe hemilobar atrophy on US. The atrophic lobe was not visible on the scintigraphic image (Fig. 2). All these patients were considered to have Hashimoto's thyroiditis, considering the hypothyroidism, detectable antithyroglobulin and/or antimicrosomal antibodies, de-

creased echogenicity on US and cytological findings. There was no difference between atrophic lobe and the contralateral one in echogenicity.

Thyroid cancer

All 5 patients (all women, age 55.2 ± 9.2 yr, range 44–67) had a postoperative histological diagnosis of papillary adenocarcinoma (PAC), and 3 of them also had follicular variant. In 4 patients there were cancer cell nests in an adenomatous goiter and occupied less than half of the HA, whereas in the remaining one patient (Fig. 3) the whole nodule corresponding to HA was occupied by cancer cells. ^{99m}Tc uptake was 2.5 ± 2.4% (n = 4). The ^{123}I uptake value at 24 h was 17.8% in one case.

Others

The incidence of thyroid hemiagenesis was approximately 0.05% in this study. Of 2 patients with thyroid hemiagenesis, one had a concomitant follicular adenocarcinoma that was not functioning. ^{99m}Tc uptake values were 0.8 ± 0.8% for EOG (n = 4) (Fig. 4), and 0.3% and 0.1% for 2 hypothyroid patients with blocking-type TSHRAb.

DISCUSSION

In the present study we found that there were scintigraphic HA not only in patients with adenoma or adenomatous goiter, but also in various other thyroid diseases. The functioning nodules accounted for 80.8% (97/120) (59 adenomatous nodules, 33 adenomas and 5 cancer) of all HA on thyroid scintigrams. This rate might be higher in iodine-deficient countries, where AFTN is almost twice as frequent as in an iodine-sufficient area such as Japan.[8]

The mechanisms of such scintigraphic features were listed by Miller et al.[9] as follows; 1) autonomous hyperfunctioning thyroid lesion, 2) tissue of relatively normal function with surrounding area of degeneration or thyroiditis, 3) a normal, hyperplastic or nodular lobe with congenital or acquired absence of the other lobe, 4) a prominently lobulated gland with sufficient asymmetry that by virtue of the greater mass alone one lobe or one area contains considerably more radioactive iodine than the other.

With regard to the comparison between ^{99m}Tc and ^{123}I scintigraphic images, the prevalence of HA in ^{123}I scans (5.7%) was higher than that in ^{99m}Tc scans (2.5%) presumably due to the biased selection of patients in the ^{123}I scan. Namely, 10 patients with HA on ^{99m}Tc scans were also examined with ^{123}I. The prevalence of reported discrepancy between ^{99m}Tc and ^{123}I scintigrams varies.[10,11] Kusic et al.[10] reported that it was found in 5–8% of thyroid nodules, twice as often in multinodular goiters as in single nodules. In this study, we saw 2 discrepant cases.

According to Studer et al.,[12] thyroid follicular cells are originally heterogeneous. During a long period of exposure to thyroid stimulators including TSH, more responsive cells are activated and proliferate, leading to the formation of hyperplastic foci, which are visualized as scintigraphic focal functioning lesions, and multiple nodules on US, and some patients with autonomously functioning nodules develop subclinical hyperthyroidism. Newly generated cells may acquire qualities not previously present in mother cells. Recently it has been reported that somatic mutations in the thyrotropin receptor and Gs-alpha gene cause the constitutive activation of the cyclic-AMP pathway in some hyperfunctioning adenomas and multiple toxic nodular goiters,[13] but the frequency of activating mutations varies (0–80%) and this theory has not reached a consensus.[14]

The prevalence of overt and subclinical hyperthyroidism in patients with a solitary functioning nodule (31.0% (22/71) including thyroid cancer) is slightly higher than that in the previous studies (17.8%[15], 21.2%[16]). In accordance with the previous studies,[8,15,16] toxic solitary nodules were significantly larger and occurred more often in older patients than in younger patients. On the other hand, the absence of cystic changes was not significantly associated with hyperthyroidism, in discordance with the study reported by Branson et al.,[16] or young age (data not shown).

Hashimoto's thyroiditis is the most frequent thyroid disorder. A variety of scintigraphic images are observed.[17–19] The homogeneous pattern is seen at the early stage, whereas advanced Hashimoto's thyroiditis shows inhomogeneous patterns including the presence of cold and hot areas. Typical US findings of Hashimoto's thyroiditis represent diffuse enlargement of the gland with decreased and inhomogeneous echogenicity reflecting histopathological changes (destruction of thyroid follicles, lymphocyte infiltration and fibrosis).[6,20] In the present study, 11 untreated patients with Hashimoto's thyroiditis including 4 with (Category 2) and 7 without (Category 3) sonographic correlating areas displayed HA. Such scintigraphic findings may be related to the extreme regional heterogeneity of pathological involvement and to various degrees of fibrosis, lymphocytic infiltration and follicular degeneration or hyperplasia.[18] Three of the 4 patients in Category 2 had a normal or slightly hypoechoic area within the noticeably hypoechoic remaining thyroid gland. We assume that a cluster of functioning thyroid cells saved from self-immunoreactive destruction or mildly destructed thyroid tissues was surrounded by much damaged thyroid tissue. The correlating area was more hypoechoic than the remaining thyroid tissue in one case. In this case, the detection of the hypoechoic area is inexplicable, but the presence of nodular hyperplasia can be speculated. Yarman et al.[19] reported that 7 (14.6%) of 48 patients with Hashimoto's thyroiditis living iodine-deficient areas had scintigraphic and US findings similar to Category 3.

Thyroid cancer is usually depicted as a cold lesion on a thyroid scntigram, and one containing a concentration of radioiodine or ^{99m}Tc-pertechnetate is considered very rare, but there have been several reports of thyroid cancer with scintigraphic hot lesions.[21–24] The frequency of malignancy including occult cancer in solitary hot nodules has ranged from 4% to 11%.[24] It was 5.3% (5/94) in our study. There was a cancer frequency of 2.5% to 3.9% for toxic nodular goiter and toxic adenoma,[24] and of 3.7% (1/28) in our study. Although most of these studies report the coexistence of occult malignancy or a small amount of malignant lesions in or close to the benign functioning tissue, providing no adequate data to confirm that the malignancy itself was the hot source, there are two well-documented reports,[21,22] where specimen autoradiography showed a high radioiodine concentration in an area of histologic thyroid adenocarcinoma. We strongly suggest that one of our cancer patients in Figure 3 has functioning cancer cells, so that the functioning nodule does not seem to preclude malignancy, requiring careful clinical management including histopathologic examinations.

We recently found the presence of localized functioning areas on thyroid scintigrams in approximately half of the patients with EOG.[7] In that study, there was no discrete nodule identified by US which correlated with the functioning area in most of the patients (5 of 7 patients with HA). In this study we found 3 (75.0%) and 1 (25.0%) of the 4 patients belonged to Category 2 and 3, respectively. We also reported that 6 of 11 hypothyroid patients with blocking-type TSHRAb had scintigraphic functioning areas and that stimulating-type TSHRAb, namely TSAb, was detected in 3 of the 6 patients.[25] In the present study, we found two such patients who belonged to Category 3. With regard to the mechanism, we speculate that chronic stimulation of the thyroid by stimulating-type TSHRAb and/or TSH might be responsible for the presence of the functioning area. In this situation, the morphological change seems to be preceded by functional change, which may account for the substantial number of patients showing Category 3 appearance. We assume similar mechanisms are involved also in patients with Hashimoto's thyroiditis and adenomatous goiter which had a Category 3 appearance, where chronic TSH stimulation might play a role. In this regard, the role of thyroid growth stimulating immunoglobulins that are detected in patients with Hashimoto's thyroiditis as well as in those with Graves' disease can also be considered.[26]

Although we often encounter mild or moderate asymmetric change in the thyroid gland on US, severe hemilobar atrophy causing such scintigraphic hot lesions as presented in this study is extremely rare. All these 3 patients were considered to have Hashimoto's thyroiditis. Fisher et al.[17] reported that 7.8% of the patients with Hashimoto's thyroiditis showed reduced appearance in one lobe on the thyroid scintigrams, but did not describe in detail the degree of reduction or the sonographic findings. The clarification of whether these patients have a rare type of Hashimoto's thyroiditis or a congenital anomaly such as hemilobar hypogenesis requires further study.[27]

Thyroid hemiagenesis, the congenital absence of one lobe, is a rare anomaly. Approximately 260 cases had been reported by 1999.[28] According to the authors, there is a 3.6 : 1 predominance of an absent left lobe vs. right lobe, and the isthmus is present in 44% of cases, when the scintigraphic appearance is known as the "hockey stick" sign.[29] Our patients did not have the "hockey stick" sign because of the absence of the isthmus. Although ^{201}Tl scintigraphy was reported to be useful for the differential diagnosis from AFTN,[30] US seems to be useful enough for the diagnosis due to its non-invasiveness, simplicity, accuracy and low economic burden.

In conclusion functioning thyroid nodules accounted for approximately four-fifths of the scintigraphic hot areas, but we should keep in mind that such lesions are observed also in patients with other thyroid diseases including autoimmune thyroid disorders, and US appears helpful clinically for the differential diagnosis.

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