Scintigraphic Findings of the Thyroid in Euthyroid Ophthalmic Graves' Disease

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The scintigraphic findings of the thyroid were analyzed in patients with euthyroid ophthalmic Graves' disease known to have some thyroid-related abnormalities. **Methods:** Technetium-99m-pertechnetate images of the thyroid from 38 euthyroid ophthalmic Graves' disease patients with small, soft or nonpalpable goiter were analyzed. **Results:** Scan images showed homogeneous (even) and nonhomogeneous (uneven) ^{99m}Tc uptake in 20 and 16 patients respectively. Poor images due to low uptake were observed in two patients. Six patients displayed alterations in scintigraphic appearance from even to uneven patterns after T3 suppression test. Statistical analysis revealed that the uneven pattern was more frequently observed in euthyroid ophthalmic Graves' disease patients than in 26 patients with hyperthyroid Graves' disease who were euthyroid during antithyroid drug therapy ($p < 0.005$). The scintigraphic heterogeneity was correlated with reduced uptake as well as a higher ratio of the uptake values after T3 treatment to the pretreatment values. Scintigraphically, hot or warm lesions were observed in most cases showing the uneven pattern (16/22; 73%). Rather low titers of antithyroglobulin, antimicrosomal antibodies and TSH-binding inhibitor immunoglobulins were detected in only 4 (10.5%), 7 (18.4%) and 12 (31.6%) patients respectively, while the prevalence of thyroid-stimulating antibodies (TSAb) was as high as 86.8% (33/38). The scintigraphic heterogeneity did not correlate with the detection of these antibodies but did correlated with the severity and duration of ophthalmopathy. **Conclusions:** The presence of functioning follicular cells with some autonomy that were heterogeneously distributed in the thyroid was observed in about half the euthyroid ophthalmic Graves' disease patients. Chronic stimulation by TSAb may be the underlying mechanism for these findings.

Key Words: euthyroid ophthalmic Graves' disease; thyroid-stimulating antibodies; thyroid scintigraphy

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When ophthalmopathy of Graves' disease occurs without hyperthyroidism, it has generally been called euthyroid ophthalmic Graves' disease. The patients often show abnormalities of thyroid function, such as a lack of suppression of radioactive iodide uptake after T3 administration and an impaired response of thyroid-stimulating hormone (TSH) to thyrotropin releasing hormone (TRH) (*1,2*). In accordance with these observations, stimulating-type TSH-receptor antibodies have been detected in a majority of the patients (*3–5*).

In this study, scintigraphic findings of the thyroid were analyzed in patients with euthyroid ophthalmic Graves' disease.

METHOD

Thirty-eight consecutive euthyroid ophthalmic Graves' disease patients were studied between 1974 and 1992. The diagnosis of euthyroid ophthalmic Graves' disease was based on Graves' ophthalmopathy in clinically euthyroid subjects with normal serum T3, T4 and free T4 concentrations. Thirteen males and 25 females were studied, all between ages 16 and 68 yr; the mean age was 45.5 ± 11.9 (mean ± s.d.) yr. None had a history of thyrotoxicosis. During follow-up, seven patients developed mild thyrotoxicosis 3.3 ± 3.2 yr later, and 1 patient developed hypothyroidism 11 yr later. The remaining 30 patients remained euthyroid during the mean follow-up period of 3.1 ± 4.1 yr.

All patients had several ophthalmic symptoms corresponding to Class II–IV in the American Thyroid Association Classification (*6*). The ophthalmopathy index (*7*) in our patients ranged from one to seven. The extent of exophthalmos was 13–27 mm and was assessed using a Hertel exophthalmometer. Nine patients without proptosis [both eyes, <18.0 mm; normal range in healthy Japanese (*8*)] had other ophthalmic symptoms such as soft-tissue involvement and ophthalmoplegia. Clinical examination, including orbital computed tomography (CT), revealed no other causes of the eye symptoms in any patients.

Goiter was not palpable in 16 patients, and the remaining 22 patients had a diffuse, small and soft goiter with a transverse diameter of less than 5 cm.

Twenty-six patients with hyperthyroid Graves' disease who had been euthyroid under treatment with antithyroid drugs for 2–5 yr served as controls (8 males and 18 females; mean age 45.6 ± 11.1 yr). Six patients with slight exophthalmos were included in this group.

The TRH test was performed in 27 patients with euthyroid ophthalmic Graves' disease by measuring serum TSH concentrations before and 30, 60 and 120 min after 500 μg intravenous TRH injection. TRH responsiveness was defined as follows: absent when both basal and TRH-stimulated TSH levels were undetectable (<0.5 mU/liter); impaired, normal and exaggerated when the peak value of TSH was 0.5–5, 5–35 and >35 mU/liter respectively.

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In these patients, the serum TSH was measured by radioimmunoassay (RIA) (normal range, <5 mU/liter). In six patients who did not undergo the TRH test, serum TSH level was determined by a sensitive IRMA (normal range, 0.3–3.9 mU/liter).

The thyroid scan was performed 30 min after intravenous injection of 74 MBq ^{99m}Tc-pertechnetate. The net thyroidal ^{99m}Tc uptake was determined by subtracting the background radioactivity just below the thyroid gland (normal range, 0.4%–3.0%) (*9*). Scan images were acquired using a gamma camera equipped with a low-energy parallel-hole collimator (Gammaview-F PC-IC-1635LF, Hitachi Medical Corporation, Chiba, Japan). Between 1000 to 2000 counts/cm^2 were collected using the 140-keV photopeak and 20% window. In five patients, ^{123}I thyroid uptake was determined at 3 and 24 hr after oral administration of ^{123}I; the image was acquired after 3 hr using a low-energy collimator.

For the 36 patients with euthyroid ophthalmic Graves' disease and all 26 euthyroid patients with treated hyperthyroid Graves' disease, imaging was repeated after 7 days of treatment with 75 μg/day of T3. These images were analyzed by clinicians with over 10 yr of experience in clinical nuclear medicine who were unaware of the clinical features and other laboratory test results. The images were classified into three groups: even, uneven and low uptake.

Ultrasonography (US) of the thyroid was performed on 11 patients using an electronic linear array real-time scanner with a 7.5 MHz transducer (Yokogawa RT 2800, Japan). Histological or cytological examination of the thyroid was performed on four patients by large-needle biopsy and on two patients by fine-needle aspiration biopsy.

Antibody titers against thyroglobulin (Tg) and thyroid microsomal antigen (M) were determined by the hemagglutination technique using commercially available kits (Fujizoki Inc., Tokyo, Japan). The titer of <100 was judged as negative for both anti-Tg and anti-M antibodies.

TSH-binding inhibitor immunoglobulins (TBII) were assayed using a commercially available kit with a minor modification (*10*). The normal range was between −11.9% and 11.0%. Thyroid-stimulating antibodies (TSAb) were assayed by a method developed in our laboratory (*11*). Cyclic AMP, produced in FRTL-5 thyroid cells exposed to immunoglobulin fractions, was measured. The normal range was <145.0%.

Data were analyzed for statistical significance by the Student's t-test, the chi-square test and by the Kruskal-Wallis test.

RESULTS

Technetium-99m Thyroid Uptake and Scintigraphic Patterns

The mean value for ^{99m}Tc uptake was 1.24% ± 1.34% in all 38 patients and 1.31% ± 1.40% in 36 patients who underwent the T3 suppression test. There was no significant decrease in ^{99m}Tc uptake after the T3 administration (1.16% ± 1.71%) when analyzed by the paired t test.

The scan image showed even and uneven uptake in 20 and 16 patients respectively (Table 1). The scintigraphic pattern could not be analyzed in the remaining two patients because low uptake produced too poor an image (<0.2%). These two patients did not undergo the T3 suppression test. Among the remaining 36 patients, the scintigraphic appearance was changed after the T3 administration from even to uneven and from even to low in six and four patients respectively. Thus, the post-T3 images consisted of 10 even, 22 uneven and 4 low uptake patterns (Table 1). Following the results of the thyroid scan, all 36 patients with euthyroid ophthalmic Graves' disease who underwent T3 suppression test were divided into three groups, as follows:

Group 1: n = 14; even before T3/even after T3 (n = 10) or even before T3/low after T3 (n = 4); not showing uneven pattern either before or after T3.
Group 2: n = 6; even before T3/uneven after T3.
Group 3: n = 16; uneven before T3/uneven after T3.

Figures 1 and 2 show representative cases categorized in

Table 1
Scintigraphic Appearance in Euthyroid Ophthalmic Graves' Disease (EOG) Compared to That in Treated Hyperthyroid Graves' Disease (HG)

Scan patterns	Number of EOG patients: Before T3 (n = 38)	Number of EOG patients: After T3 (n = 36)	Number of HG Patients: After T3 (n = 26)
Even	20 (52.6%)	10 (27.8%)	22 (84.6%)
Uneven	16 (42.1%)	22 (61.1%)*	4 (15.4%)*
Low[§]	2 (5.3%)	4 (11.1%)	0 (0%)

*$p < 0.005$ analyzed with chi-square testing[§]. Poor images are a result of low ^{99m}Tc uptake (<0.2%) which made the analysis impossible. Twenty-four patients and two patients with treated HG exhibited even and uneven uptakes, respectively, before T3 administration (mean uptake 2.8% ± 1.9%).

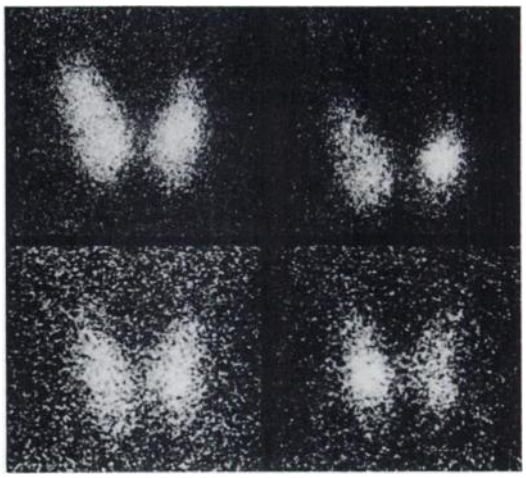

FIGURE 1. Technetium-99m thyroid scintigrams from Group 2 patients ("even" before T3; "uneven" after T3). (Upper Panel) Y.T., a 43-yr-old female; ^{99m}Tc uptake is 1.1% before T3 (left) and 0.6% after T3 (right). There is a diffuse small goiter (4.5 cm) and diffuse normal echogenicity with a small hypoechoic mass (1.0 cm) in the right lobe on ultrasound; TSAb 1270%. (Lower Panel) C.U., a 34-yr-old female; ^{99m}Tc uptake is 0.5% before T3 (left) and 0.4% after T3 (right). The goiter is not palpable; TSAb 177%.

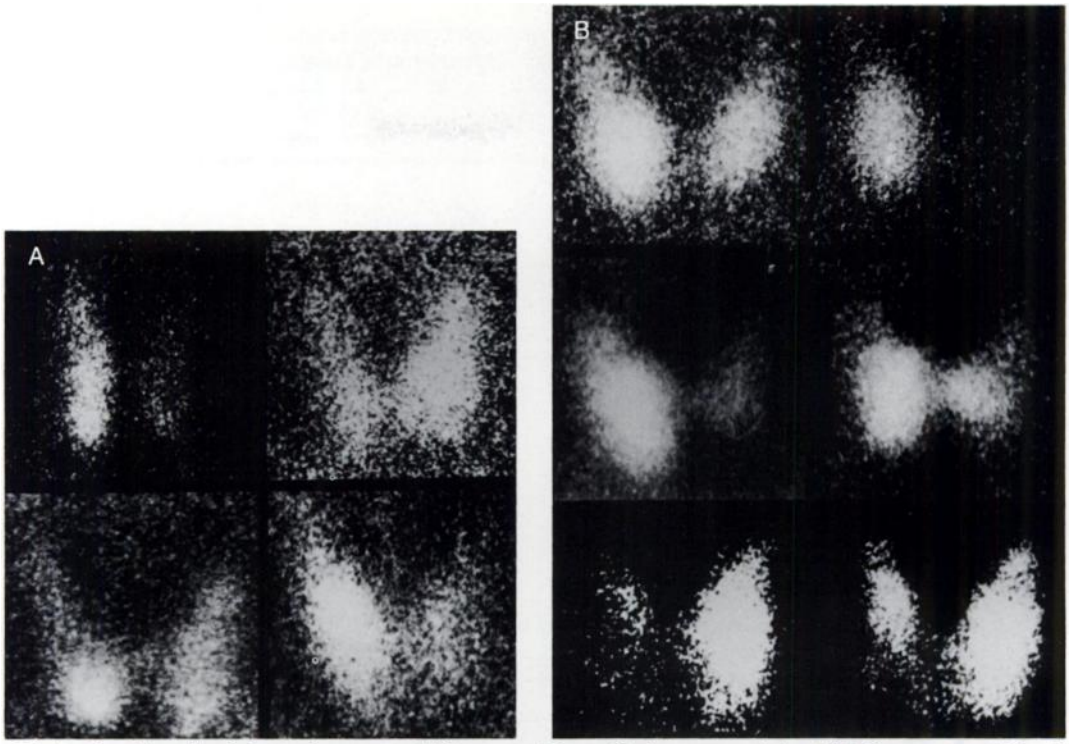

FIGURE 2. Technetium thyroid scintigram in representative cases (Group 3) of uneven uptake. (A) left upper panel: Yas.K., a 32-yr-old female; ^{99m}Tc uptake after T3 is 0.2% (before T3 0.4%). The goiter is not palpable. There is diffuse normal echogenicity on ultrasound; TBII 15.7%, TSAb 161%. Right upper panel: Yo.K., a 32-yr-old male; ^{99m}Tc uptake after T3 is 0.7% (before T3 0.7%), goiter is not palpable; TSAb 491%. Left lower panel: T.S., a 47-yr-old male; ^{99m}Tc uptake after T3 is 0.4% (before T3 0.5%). There is a small diffuse goiter (4.4 cm). There is a diffusely enlarged goiter with normal echogenicity on ultrasound; TSAb 1490%. Right lower panel: I.N. a 44-yr-old female; ^{99m}Tc uptake after T3 is 0.4% (before T3 0.4%). The goiter is not palpable; TSAb 1310%. (B) Upper panel: H.Y. a 53-yr-old male; ^{99m}Tc uptake before T3 is 0.4% (left) 0.6% after T3; three years later it is 0.6% before T3 (right) and T3 0.7% after T3. The goiter is not palpable; there is an ill-defined hypoechoic area in the right lobe. TBII 24.1%; TSAb 1067%. Middle panel: T.T. a 45-yr-old female; ^{99m}Tc uptake after T3 is 0.9% (left) and 0.8% before T3; two years later it is 0.5% after T3 (right) and 0.4% before T3. There is a diffuse small goiter (4.0 cm); TSAb 380%. Lower panel: Yae.K. a 40-yr-old female, ^{99m}Tc uptake is 1.2% (left) at the initial visit and ^{123}I uptake is 34.4% at 3 hr (right) 3 yr later at the time of mild thyrotoxicosis and 59.7% 24 hr after oral administration of 3.7 MBq ^{123}I. There are a diffuse small goiter (4.1 cm), a well-defined hypoechoic lesion in the left lobe corresponding to the hot lesion (histology: epithelial hyperplasia) and small cystic lesions with inhomogeneous echogenicity in the left lobe on ultrasound. TBII 20.6%; TSAb 289%.

Groups 2 and 3. The thyroid scan obtained after T3 treatment revealed emergence of an apparently warm lesion in two of six patients (Y.T. and C.U. in Fig. 1) classified into Group 2. The scintigraphic heterogeneity observed in 14 of 16 patients classified into Group 3 was characterized by the presence of warm or hot lesions. These lesions were not suppressed by T3 treatment (Fig. 2a). Comparison of the scan image before T3 with that after T3 in all Group 3 patients revealed no apparent change in 11 patients. In the remaining five patients, warm lesions became more clearly visible after T3 treatment.

Comparison of the images obtained after T3 treatment in the euthyroid ophthalmic Graves' disease patients with those images in the euthyroid patients with treated hyperthyroid Graves' disease who showed similar uptake values (1.16% ± 1.71% versus 0.93% ± 0.80%) revealed that uneven uptake was more frequently observed in euthyroid ophthalmic Graves' disease patients ($p < 0.005$, chi-square test) (Table 1).

Comparison of ^{99m}Tc uptake values in these three groups revealed that the overall reduced uptake and the higher ratio of the uptake values after T3 treatment to pretreatment values (post-T3/pre-T3 ratio) were correlated with the scintigraphic heterogeneity (Table 2). Table 3 shows the ^{99m}Tc thyroid uptake values in the presence or absence of focal lesions with increased radioactivity. The presence of hot or warm lesions was correlated with lower uptake values and with higher post-T3/pre-T3 ratios.

During follow-up, imaging was repeated in 15 patients after a mean observation period of 3.7 ± 2.7 yr (six in Group 1, two in Group 2, and seven in Group 3). Eleven patients (five in Group 1, one in Group 2, and five in Group 3) exhibited no apparent change in scintigraphic appearance. The thyroid uptake became uneven in one patient in Group 1. One patient in Group 2 (Y.T. in Fig. 1), who had a focal lesion with increased radioactivity in the left lobe seen after T3 treatment, developed hypothyroidism 11 yr later when the lesion in the left lobe disappeared and a new focal lesion emerged in the upper pole of the right lobe. Figure 2B shows the changes in scintigraphic appearance in two patients in Group 3 (i.e., presence of a warm lesion followed by a hot lesion (H.Y.) and increase in number of

Table 2
Thyroid Uptake Values, Ophthalmopathy Index, TBII, TSAb, Antithyroglobulin and Antimicrosomal Antibodies in Three Groups of Patients with Euthyroid Ophthalmic Graves' Disease

	Group 1 (even/even or low)	Group 2 (even/uneven)	Group 3 (uneven/uneven)
No. of patients	14	6	16
Age (yr)	41.7 ± 14.9†	49.5 ± 9.0	46.5 ± 9.0
^{99m}Tc uptake*			
Before T3 (%, a)	1.94 ± 1.71	1.87 ± 1.08	0.53 ± 0.26
After T3 (%, b)	1.54 ± 2.19	1.82 ± 2.02	0.49 ± 0.27
Ratio (a/b)**	0.61 ± 0.42	0.82 ± 0.37	1.00 ± 0.47
Ophthalmopathy Index§	1.86 ± 1.06	3.83 ± 1.33	3.63 ± 1.74
TBII activity (%)	7.6 ± 15.8	1.6 ± 10.3	6.6 ± 12.6
Prevalence (%)	35.7 (5/14)	16.7 (1/6)	37.5 (6/16)
TSAb activity (%)	917 ± 2145	1102 ± 918	604 ± 512
Prevalence (%)	71.4 (10/14)	100.0 (6/6)	93.8 (15/16)
anti-Tg titer (x)	neg-1600	neg-320	neg-100
Prevalence (%)	7.1 (1/14)	16.7 (1/6)	6.3 (1/16)
anti-M titer (x)	neg-25600	neg-1280	neg-640
Prevalence (%)	35.7 (5/14)	16.7 (1/6)	6.3 (1/16)

†Mean ± s.d. Tg = thyroglobulin; M = microsomes. Technetium-99m uptake before T3 (a) (*), the ratio (a/b) (**) and ophthalmopathy index (§) are significantly different among the three groups ($p < 0.005$, $p < 0.05$ and $p < 0.005$, respectively) when evaluated by Kruskal-Wallis one-way analysis. The normal range: ^{99m}Tc uptake (30 min), 0.4-3.0%; TBII, −11.9–11.0%; TSAb, < 145%; anti-Tg, <100; anti-M, <100. The TSAb-negative patient in Group 3 had a positive titer of anti-M at ×640.

hot areas from one to two (T.T.)). In all four patients (two in Group 1, one in Group 2, and one in Group 3) who developed mild thyrotoxicosis and underwent repeated scanning at the time of hyperthyroidism, ^{99m}Tc thyroid uptake was increased without any change in scintigraphic pattern.

In five patients with uneven uptake, the ^{123}I image was similar to the ^{99m}Tc image. A representative case (Yae. K.) is shown in Figure 2b.

Relationship of Scintigraphic Pattern to Sonographic and Histological Findings

The sonographic findings were normal in 7 (two in Group 1, one in Group 2, and four in Group 3) of the 11 patients (two in Group 1, three in Group 2, and six in Group 3) who underwent thyroid US. These four patients in Group 3 (including Yas. K. and T.S. shown in Fig. 2a) had a scintigraphic hot or warm lesion, where no abnormal echogenicity was observed. One patient in Group 2 showed the presence of multiple, small hypoechoic areas. Another patient in Group 2 (Y.T. in Fig. 1) had a small hypoechoic lesion in the right lobe, later found to be benign (Pap. I) by fine-needle aspiration biopsy. However, the patient had normal sonographic findings in the left lobe where a T3-nonsuppressible hot lesion was noted. One patient in Group 3 (H.Y. in Fig. 2b) showed an ill-defined hypoechoic area in the right lobe in which a hot lesion was present. Another patient in Group 3 (Yae. K. in Fig. 2b) had a well-defined hypoechoic lesion corresponding to a hot lesion. The patient's histological study, using fine-needle aspiration biopsy, revealed epithelial hyperplasia. Thus, the sonographic abnormality was found in only two of seven lesions with increased radioactivity. Diffuse hypo-

Table 3
Technetium-99m Thyroid Uptake Values, Ophthalmopathy Index and TSAb in Patients with Euthyroid Ophthalmic Graves' Disease with and without Scintigraphic Hot or Warm Lesions

Hot or warm lesions (+)	No. of patients	^{99m}Tc uptake		Ratio (a/b)	Ophthalmopathy index	TSAb (%) (prevalence)
		Before T3 (%, a)	After T3 (%, b)			
(+)	16* (44%)	0.53 ± 0.28‡	0.49 ± 0.24¶	0.93 ± 0.35§	3.75 ± 1.71‡	655 ± 519 (15/16; 93.8)
(−)	20** (56%)	1.91 ± 1.55	1.64 ± 2.09¶	0.68 ± 0.42§	2.35 ± 1.31‡	93 ± 1856 (17/20; 85.0)

Presence or absence of the focal lesion with increased radioactivity was determined by analysis of the image after T3 treatment. *Two patients from Group 2 and 14 patients from Group 3 were included. †Fourteen patients from Group 1, four patients from Group 2 and two patients from Group 3 were included. ‡$p < 0.005$, § $p < 0.025$, ¶$p < 0.05$.

echogenicity, typical of advanced Hashimoto's thyroiditis (HT) (*12*), was not noted in any of the patients tested.

Large-needle biopsy was performed in four patients (one in Group 1, one in Group 2, and two in Group 3). In the two patients in Group 3, the histology of thyroid tissues obtained from a portion corresponding to a scintigraphic warm lesion was epithelial hyperplasia and normal thyroid appearance. These two patients had negative antibody titers against both Tg and M as well as negative TBII activities, but had positive TSAb activities (392% and 1310%; I.N. in Fig. 2a). Histological findings in 2 cases (one in Group 1: negative anti-Tg, anti-M and TBII, TSAb 165%; and the other in Group 2: anti-Tg ×400, anti-M ×1280, TBII 15.3%, TSAb 351%) were normal thyroid and diffuse epithelial hyperplasia with minimal degenerative changes. Lymphocytic infiltration or fibrosis was not detected.

Relationship between Scintigraphic Pattern and Ophthalmopathy

The ophthalmopathy index was correlated with unevenness of the scan images (Table 2). As shown in Table 3, the presence of hot or warm lesions was also correlated with the ophthalmopathy index. As for the relationship between the scintigraphic findings and the duration of ophthalmopathy, 4 patients in Group 1 and 12 patients in Group 3 had a history of illness longer than 6 mo, while 10 in Group 1 and 4 in Group 3 had noticed their eye problems within 6 mo before their first visit. Thus, patients with uneven uptake had a longer history of illness ($p < 0.05$, chi-square test).

Relationship between Scintigraphic Pattern and TSH Responsiveness to TRH Stimulation

Among the 27 patients who underwent the TRH test, 11 patients displayed no response, 6 patients displayed impaired response, and 10 patients displayed normal response. Among the 11 patients with no response, 5 showed even uptake (Group 1), 4 showed uneven uptake (Group 3), and 2 patients belonged to Group 2. Among the 6 patients with impaired response to TSH, 1 patient belonged to Group 2 and 5 patients belonged to Group 3. Of the 10 patients with normal response, 7 had even uptake (Group 1), 2 had uneven uptake (Group 3) and 1 imaged poorly because of low uptake. Thus, the scintigraphic patterns did not correlate with TSH responsiveness to TRH stimulation.

The serum TSH level determined by IRMA was low in one patient (Group 1) and normal in five patients (one in Group 1, one in Group 2, and three in Group 3).

Relation to Thyroid-related Antibodies

Anti-Tg, anti-M, TBII and TSAb were determined in all 38 patients. Anti-Tg and anti-M were detectable in only 4 (10.5%) and 7 (18.4%) patients respectively, and the titers were rather low. There was no significant correlation between anti-Tg and anti-M titers and the scintigraphic patterns (Table 2).

However, TBII and TSAb were detected in 12 (31.6%) and 33 (86.8%) patients respectively. These activities did not differ significantly if the uptake was even or uneven (Table 2), or if there was or was not a functioning lesion (Table 3). One TSAb-negative patient in Group 3 had a small warm lesion (negative TBII, ^{99m}Tc uptake 0.5% before T3 and 0.6% after T3).

TSAb activity was correlated with the ophthalmopathy index ($r = 0.453$, $p < 0.005$) (data not shown).

DISCUSSION

Scintigraphic findings of the thyroid affected by HT are characterized by low and uneven uptake of radioiodine or ^{99m}Tc in advanced cases, but characterized by even uptake in most of the less advanced cases (*13*). The distribution of the radioisotopes in the thyroid gland affected by hyperthyroid Graves' disease is homogeneous in most of the cases (*13*), as demonstrated in the patients treated with antithyroid drugs. In contrast to HT and hyperthyroid Graves' disease, there have been no studies in which the scintigraphic appearance was analyzed in a large population of euthyroid ophthalmic Graves' disease patients.

The thyroid gland of euthyroid ophthalmic Graves' disease patients has been reported to be impalpable or slightly and diffusely enlarged (*1,3,4,14,15*). Although the histological diagnosis of HT has been documented in some patients (*1,2*), most patients have negative or low anti-Tg and anti-M titers (*3–5,15*). In a study by Kosugi et al. (*15*), histological examination revealed only slight inflammatory or degenerative changes in two of the nine patients. Euthyroid ophthalmic Graves' disease is similar to hyperthyroid Graves' disease because TSH receptor antibodies are present in the serum (*3–5,11*). With this clinical background, we had expected most patients with euthyroid ophthalmic Graves' disease to show a homogeneous scintigraphic appearance with a normal-sized or slightly enlarged thyroid gland. However, as many as 61% of the patients exhibited uneven uptake after T3 treatment. Statistical analysis revealed that uneven uptake was more frequently observed in euthyroid ophthalmic Graves' disease patients than in hyperthyroid Graves' disease patients treated with antithyroid drugs. This comparison was made with those who showed similar uptake values, because any image with low uptake appears less homogeneous.

The association of unevenness to overall reduced uptake indicates impaired function of the thyroid follicular cells. The concomitant presence of advanced HT, however, is not likely a major cause of the scintigraphic heterogeneity in that:

1. There were low or negative anti-Tg and anti-M titers.
2. There was no significant difference in titers or prevalence of these antibodies between even and uneven groups.
3. Small, soft goiter are rarely palpable in patients with advanced HT.
4. Sonographic and histological findings obtained in some patients showed no inflammatory changes.

5. Hot or warm lesions are infrequently observed in HT.

Antibody-dependent, cell-mediated cytotoxicity and antibody-dependent, complement-mediated cytotoxicity against thyroid cells demonstrated in euthyroid ophthalmic Graves' disease patients (*16*) may play an important role in the mechanism of the reduced uptake. As an alternative, the effects of cytokines such as IL1, TNF-α, and IFN-γ, which are known to inhibit ^{125}I organification (*17*), remain to be elucidated.

Scintigraphic hot or warm lesions resistant to T3 suppression were observed in most cases of uneven uptake (2 of 6 in Group 2, and 14 of 16 in Group 3). Furthermore, the ratio of uptake values after T3 treatment to pretreatment values was significantly higher in patients with uneven uptake than in patients with even uptake. The unevenness was noted only after T3 treatment in some patients (Group 2). These findings indicate that TSH independently functioning follicular cells heterogeneously distributed in the thyroid are primarily responsible for the scintigraphic unevenness. When small clusters of functioning follicular cells are present in the thyroid, the scintigraphic appearance is heterogeneous. On the other hand, a larger cluster of these cells causes overproduction of thyroid hormones, leading to reduced ^{99m}Tc uptake (because of decreased serum TSH levels and inactivation of the surrounding tissues) and finally to the appearance of a hot lesion. In accordance with these clinical features of euthyroid ophthalmic Graves' disease, there is one case report in which a patient with euthyroid ophthalmic Graves' disease had a solitary hot nodule (*18*).

The scintigraphic appearance in typical cases of euthyroid ophthalmic Graves' disease with uneven uptake resembles that of multinodular goiter. Normal thyroid tissues are originally heterogeneous. Normal or even "cold" follicles coexist with small clusters of follicles with a certain degree of autonomous function (*19*). In the course of goitrogenesis, overt or subclinical thyrotoxicosis—a common finding in Plummer's disease or multinodular goiter (*20*)—occurs over a period of several years as the hot lesions increase in size.

TSAb activity significantly correlated with the ophthalmopathy index. Gupta et al. (*21*) reported that Graves' ophthalmopathy was closely linked to TSAb but not to TBII, in patients with Graves' disease. Cell-mediated immunity and cytotoxic antibodies against shared thyroid and orbital antigens—a plausible explanation for the association of ophthalmopathy with autoimmune thyroid diseases—has been postulated (*16,22,23*). However, there is no evidence for a pathogenetic role of TSAb that cross-react with eye muscle or orbital fibroblasts.

The presence of TSAb in a majority of the euthyroid ophthalmic Graves' disease patients, together with the correlation between TSAb and the severity or the duration of ophthalmopathy, indicates that most euthyroid ophthalmic Graves' disease patients with a long history of illness might have possessed TSAb in their serum over a long period. During this period, TSH receptor antibodies with positive TSAb activity but negative or only weakly positive TBII activity were not potent enough to cause thyrotoxicosis (*3,4,24*). Chronic mild stimulation by the antibodies may trigger only more responsive follicles, resulting in the nonhomogeneous scintigram—namely, the presence of warm or hot lesions. In classic Graves' disease, however, acute intense stimulation by TSH receptor antibodies with potent TSAb and TBII activities causes activation of all follicles, showing diffusely increased uptake of ^{99m}Tc or radioiodine (*25*). On the other hand, TSAb in euthyroid ophthalmic Graves' disease patients may have increased the turnover rate of normal cells, resulting in the presence of a variety of cells not normally seen in adult life, including hyperfunctioning and nonfunctioning cells.

The possible role of TSAb was further supported by both the histological or cytological finding of thyroid tissues obtained from a scintigraphic hot lesion in some patients and by the changes in scintigraphic appearance during the follow-up period (Fig. 2).

Comparison of US and scintigraphic findings revealed that five of seven hot or warm lesions were not accompanied by sonographic abnormalities. This suggests that the morphological change (i.e., formation of nodule(s) detected by US) was preceded by the functional change (i.e., formation of hot or warm lesions detected by thyroid scintigraphy) (*19*). These T3-nonsuppressible functioning lesions or nodules may not necessarily be autonomous, since TSAb detected in most patients with functioning lesions (15/16) are nonsuppressible. However, some patients showed a focal area of increased radioactivity that was newly identified or more clearly visible after T3 treatment, suggesting that the follicular cells in these patients have autonomous function.

In Marine-Lenhart syndrome, hyperthyroid Graves' disease patients have a functioning nodule (*26*). Although it is unknown whether TSAb are pathogenetically involved in the formation of functioning nodules in this syndrome, the production of TSH receptor antibodies by plasma cells in inflammatory infiltrates that surround a hot nodule was recently demonstrated (*27*).

One TSAb-negative patient in Group 3 had slightly uneven uptake and a small area of increased ^{99m}Tc uptake. It is possible that TSAb were not sufficiently produced by lymphocytes to be detected in the circulation. Paschke reported that thyroid epithelial cells in Graves' disease near the lymphocyte aggregates were regionally stimulated, as evaluated by measurement of the cell nuclear volume (*28*). Alternatively, the warm lesion in this patient may have been autonomously functioning. The TSH stimulation test, which was not performed, would be necessary to demonstrate the presence of concurrent autonomous tissue in euthyroid ophthalmic Graves' disease patients.

The scintigraphic appearance of the thyroid in euthyroid ophthalmic Graves' disease was characterized by both the uneven uptake in 61% of the cases and by the presence of hot or warm lesions in 44% of the cases. Euthyroid oph-

thalmic Graves' disease can be a differential diagnosis when such heterogeneous scan patterns are seen.

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