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Atypical Clinical Courses of Graves' Disease Confound Differential Diagnosis of Hyperthyroidism

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Background: This study examined the appropriateness of the current paradigm for differential diagnosis of painless thyroiditis and Graves' disease (GD) in patients with thyrotoxicosis.

Methods: We retrospectively evaluated the clinical course of 343 consecutive patients with hyperthyroidism diagnosed by Tc-99m pertechnetate thyroid uptake (TcTU) testing at our hospital from January 2011 to December 2017.

Results: Of the 263 patients with normal or high TcTU levels (≥1.0%), 255 (97%) had unequivocal GD and 5 had spontaneous remission GD or atypical GD. Of the 10 patients with low TcTU levels (<1.0% and ≥0.5%), 7 had GD, while others had subclinical GD, spontaneous remission GD with later relapse, and painless thyroiditis. Of those with very low TcTU levels (<0.5%), most had thyroiditis (painless thyroiditis, 33/67 [49%]; subacute thyroiditis, 29/67 [43%]), and some were positive for anti-TSH receptor antibodies.

Conclusion: Given that atypical GD may confound the diagnosis of thyrotoxicosis, it is essential to follow the patient as a tentative diagnosis, whatever the diagnosis. This is the first report clearly demonstrating that so far there is no gold standard for the diagnosis of GD. It is therefore urgent to establish a consensus on the definition of GD so that the specificity and sensitivity of future diagnostic tests can be determined. (J Nippon Med Sch 2024; 91: 48–58)

Key words: Tc-99m pertechnetate, thyrotoxicosis, hyperthyroidism, autoimmune thyroid disease, Graves' disease

Introduction

Graves' disease is the most common cause of hyperthyroidism and can have serious adverse health effects if not properly treated[1–3]. Because treatment of Graves' disease with anti-thyroid drugs (ATD) occasionally results in serious side effects such as agranulocytosis, liver damage, and arthritis[4–6], accurate diagnosis is important. Graves' disease is usually diagnosed when a patient presents with symmetrically enlarged thyroid, recent onset of orbitopathy, and positivity for thyrotropin receptor antibodies (TRAb). When the diagnosis is unclear, further evaluation of radioactive iodine uptake or Tc-99m pertechnetate scans and uptake is recommended[7–11].

Although many studies support current criteria for differential diagnosis of painless thyroiditis and Graves' disease[12–14], there are a small but non-negligible number of patients whose diagnosis remain in question even after undergoing various diagnostic tests, suggesting that it is not always possible to definitively differentiate painless thyroiditis from Graves' disease. This should prompt a rethinking of the current diagnostic paradigm, which regards these conditions as distinct disease entities. This

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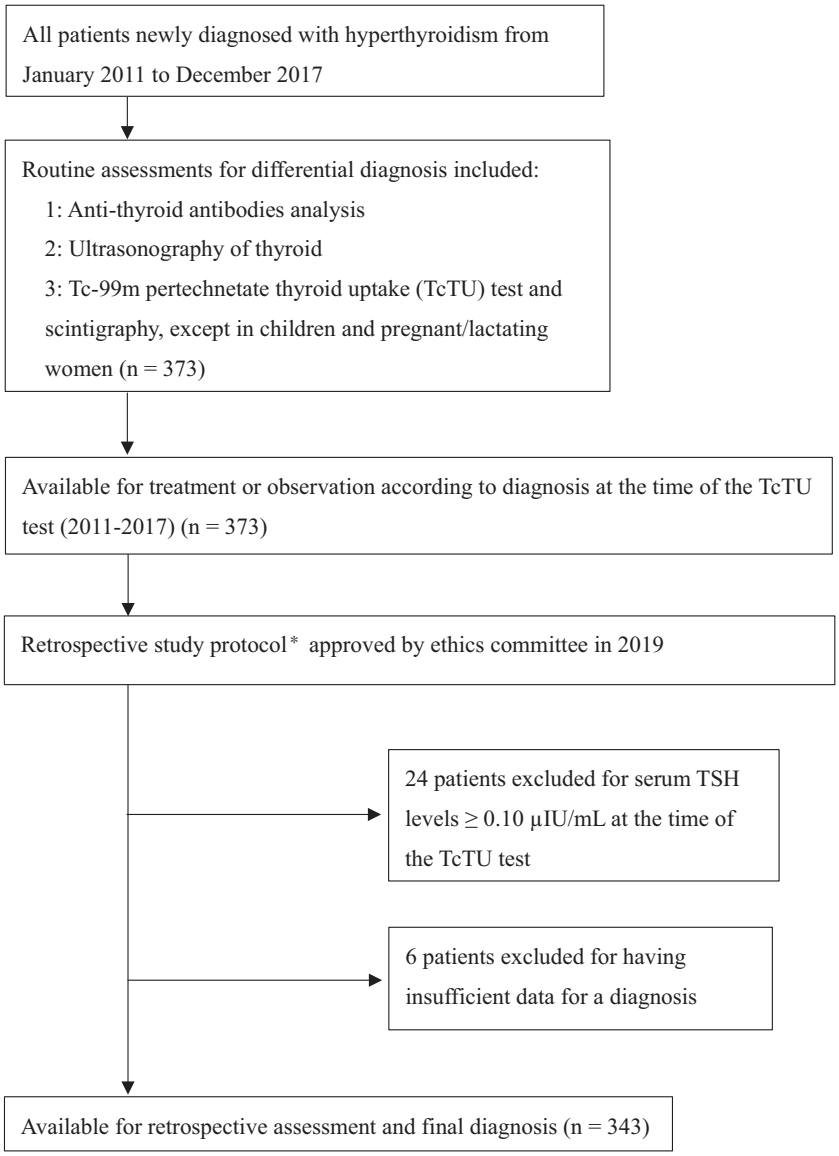

Fig. 1 Study Flowchart
* The study protocol is described in the text.

study aimed to identify the causative diseases of hyperthyroidism by using the TcTU test to determine whether the current paradigm is appropriate for diagnosis of hyperthyroidism.

Materials and Methods

Patients

From 2011 January to 2017 December, all patients who received a diagnosis of suspected hyperthyroidism, except pregnant/lactating women and children, underwent TcTU testing for hyperthyroidism (**Fig. 1**) at Chiba Hokusoh Hospital, Nippon Medical School, in Japan. A total of 373 patients were diagnosed with hyperthyroidism during this period. In 2019, the protocol of this retrospective study was approved by the relevant ethics committee. Twenty-four patients with serum thyroid stimulating hormone (TSH) levels above the detection threshold (≥0.10 μIU/mL) and 6 patients with missing laboratory data were excluded. Data for the remaining 343 patients were analyzed.

Laboratory Assessment

Laboratory assessment of thyroid function involved measuring serum levels of TSH, free triiodothyronine (FT3), free thyroxine (FT4), TSH binding inhibitory immunoglobulin (TBII), thyroid-stimulating antibody (TSAb), thyroid peroxidase antibody (TPOAb), and thyroglobulin antibody (TgAb). Serum levels of TSH, FT3, and FT4 were measured by enzyme immunoassay (AxSYM; Abbot, Tokyo, Japan; from January 1, 2011 to March 31, 2013) (TSH reference range, 0.49-4.67 μIU/mL;

FT3 reference range, 1.45-3.48 pg/mL; and FT4 reference range, 0.71-1.85 ng/dL) or chemiluminescent immunoassay (ARCHITECT i1000SR; Abbot, Tokyo, Japan; from April 1, 2013 to December 31, 2017) (TSH reference range, 0.35-4.94 μIU/mL; FT3 reference range, 1.71-3.71 pg/mL; and FT4 reference range, 0.70-1.48 ng/dL). TBII was measured by radioreceptor assay using the Yamasa DYNOtest TRAb Human kit (Yamasa, Chiba, Japan; reference range, <1.0 IU/L). TSAb were measured by bioassay and radioimmunoassay using the Yamasa TSAb kit (Yamasa, Chiba, Japan; from January 1, 2011 to March 29, 2015; TSAb reference range, <180%) or by bioassay and enzyme immunoassay using the Yamasa EIA TSAb kit (Yamasa, Chiba, Japan; from March 30, 2015 to December 31, 2017; TSAb reference range, ≤120%). TPOAb and TgAb were measured by electrochemiluminescence immunoassay (Roche Diagnostics K. K., Basel, Switzerland; TPOAb reference range, <16.0 IU/mL; TPOAb detectable level, <5.0 IU/mL, ≥600 IU/mL; TgAb reference range, < 28.0 IU/mL; TgAb detectable level, <10.0 IU/mL, ≥4,000 IU/mL).

Tc-99m Pertechnetate Thyroid Uptake

The TcTU test was performed on the day of or within 1 month of the thyrotoxicosis diagnosis. Thyroid scintigraphy using a scintillation camera (BRIGHT VIEW, Philips Electronics Japan, Tokyo, Japan) was conducted 20 minutes after intravenous injection of 370 MBq (10 mCi) of Tc-99m pertechnetate. Images of the syringe were acquired before and after radiopharmaceutical injection. The number of counts present in the thyroid gland was determined by outlining a manual region of interest (ROI) drawn around the borders of the gland. Another ROI was drawn on the right side of the chest for background subtraction. On the basis of thyroid and syringe counts corrected for acquisition time and Tc-99m decay, uptake was calculated by using the following equation and expressed as a percentage of dose: Tc-99m uptake (%) = (TC − BC × TP/BP) × 100/IC (TC = counts in thyroid ROI, TP = thyroid ROI pixels, BC = counts in background ROI, BP = background ROI pixels, and IC = corrected injection counts).

Study Protocol

The protocol of this retrospective study was approved by the ethics committee of Nippon Medical School Chiba Hokusoh Hospital (No. 746) and conformed to the provisions of the Declaration of Helsinki. Informed consent was obtained from the patients who were treated in the hospital in 2019. A waiver of informed consent was approved for other patients who were lost to follow-up before 2019. Requirements for the approval of the waiver were that (1) the research involved no more than minimal risk; (2) the waiver of informed consent would not adversely affect the rights or welfare of the patients; (3) information on the research project was open to the public through the bulletin board of the hospital, including its website; and (4) all patients had a right to opt out any time before publication of the study data.

Initial diagnoses were made in accordance with the guidelines of the Japan Thyroid Association[15], the American Thyroid Association, and European Thyroid Association[7,16]. Currently, the English version of the diagnostic guideline posted on the website of the Japan Thyroid Association is available as of June 2022 (Supplemental Table 1), and the diagnostic guideline as of 2011 is nearly identical to this guideline. The initial diagnosis was based mainly on criteria 1) of this diagnostic guideline, ie, Graves' disease was diagnosed based on the presence of thyrotoxicosis, positivity for TBII or TSAb, and elevated TcTU values. On the basis of our previous results[17], the cut-off TcTU value for distinguishing between Graves' disease and painless thyroiditis was set to 0.9%, and a TcTU value of 1.0% or more was diagnosed as Graves' disease. Painless thyroiditis was diagnosed by the presence of thyrotoxicosis without thyroid gland pain, spontaneous improvement of thyrotoxicosis within 3 months, and a low TcTU value (<0.9%). Subacute thyroiditis was diagnosed by the presence of thyrotoxicosis, swelling with pain and tenderness in the thyroid gland, an elevated C-reactive protein or erythrocyte sedimentation rate, and an ultrasonography-confirmed hypoechoic lesion at the painful portion of the thyroid gland. Autonomously functioning thyroid nodule (AFTN) was diagnosed by the presence of non-autoimmune thyrotoxicosis and a thyroid nodule, along with strong accumulation consistent with decreased uptake of thyroid tissue around the nodule in the TcTU test.

Final diagnoses were retrospectively made for all patients on the basis of their clinical course. Patients with normal FT3 and FT4 levels, and those with serum levels of TSH that continued to be undetectable for 3 months or longer, were categorized as having subclinical Graves' disease. Those with spontaneous resolution of Graves' disease, subclinical Graves' disease, questionable Graves' disease, and Graves' disease with subacute thyroiditis[18,19] were categorized respectively and excluded from the category Graves' disease. The "others" category included amiodarone-induced thyrotoxicosis[20], overdose of thyroid hormone medication, and gestational transient hyperthy-

roidism.

Statistical Analysis

Categorical variables are expressed as numbers, and continuous variables are described as mean ± SD or maximum/minimum levels. All analyses were performed using JMP software (version 14.2; SAS Institute Inc., Cary, North Carolina, USA).

Results

Table 1 shows the biochemical characteristics of patients, categorized by final diagnosis and TcTU levels. Of the 263 patients with normal or high TcTU levels (≥1.0%), 255 (97%) had Graves' disease with typical symptoms and clinical data that were consistent with those described in the guidelines. Of the other patients with a TcTU level ≥1.0%, 4 had Graves' disease that spontaneously remitting without treatment (cases 1-4). The biochemical characteristics and clinical courses of these 4 patients are shown in **Table 2a** and **Table 2b**. These patients had very minor or no symptoms, leading their attending physicians to choose observation without treatment. Two patients each were TRAb-positive and TRAb-negative. Of the patients with a TcTU level ≥1.0%, 1 (case 5) had atypical Graves' disease characterized by elevated serum FT3 and FT4 levels at initial diagnosis that spontaneously returned to within the normal ranges after about 3 weeks, and a consistently undetectable TSH. This patient developed overt hyperthyroidism 7 months later and was started on methimazole. The others had Graves' disease complicated by subacute thyroiditis (case 6), and AFTN; 1 patient was found to be pregnant.

Among those with low TcTU levels (<1.0% and ≥0.5%), 7 were retrospectively diagnosed as having Graves' disease. For cases 9-13, serum TSH was below the detection threshold at 3 or more months later. In case 8, methimazole treatment was started immediately after the TcTU test, because of critical heart failure, and hyperthyroidism resolved and did not recur, which made it impossible to confirm the diagnosis of Graves' disease but suggested instead painless thyroiditis, given the extremely rapid disease resolution with methimazole. In case 14, hyperthyroidism was confirmed 3 months after the TcTU test, which suggested a diagnosis of Graves' disease, despite the subsequent loss to follow-up. In case 15, spontaneously remitting Graves' disease was suspected, while hyperthyroidism relapsed 15 months later. Another patient was classified as having subclinical Graves' disease (case 16), because the patient developed overt hyperthyroidism 5 months later. Among those with low TcTU levels, 1 patient had typical painless thyroiditis consistent with that described in the guidelines.

Of the 67 patients with very low TcTU levels (<0.5%), most were classified as having painless thyroiditis (33/67; 49%) or subacute thyroiditis (29/67; 43%); none was suspected of having Graves' disease, and some patients were positive for TBII or TSAb.

Discussion

Sequelae of untreated thyrotoxicosis include atrial fibrillation, embolic events, neuropsychiatric symptoms, cardiovascular collapse, and, rarely, death[21–23]. Of the diseases that cause thyrotoxicosis, Graves' disease is the most common. ATD, radioactive iodine (RAI) therapy, and surgery are the treatments of choice for Graves' disease. ATD have been associated with rare but fatal adverse effects, such as agranulocytosis and liver damage, and RAI therapy and surgery are likely to irreversibly affect the thyroid. Thus, accurate diagnosis of Graves' disease is important for avoiding unnecessary treatment. However, definitive diagnosis of hyperthyroidism is not always straightforward, especially when Graves' disease must be differentiated from painless thyroiditis.

Although painless sporadic thyroiditis and painless postpartum thyroiditis are essentially the same disease, the latter is associated with pregnancy and is closely related to autoimmune Hashimoto thyroiditis[24]. In typical cases, the disease is self-limiting, and the thyrotoxic phase continues for 3-4 months and is followed by the hypothyroid phase.

The TcTU test is accepted as definitive for distinguishing Graves' disease from painless thyroiditis; however, thyroid scintigraphy is available at only a limited number of centers and not on all patients with hyperthyroidism undergo thyroid scintigraphy even at these centers. In addition, the cut-off value for differentiating these diseases is not standardized and is at the discretion of the center.

Uchida et al.[12] reported a sensitivity of 96.6% and a specificity of 97.1% for differentiating Graves' disease and painless thyroiditis with a TcTU test cut-off value of 1.0%; however, in that study, Graves' disease and painless thyroiditis were diagnosed after a review of all clinical data by 3 experienced endocrinologists, which suggests that the current path for diagnosis depends largely on empirical decisions. Zuhur et al.[13] reported a sensitivity of 90.7% and a specificity of 89.9% for differentiating Graves' disease and silent thyroiditis with a TcTU test cut-off value of 3.0%. Likewise, many studies used the

Table 1 Biochemical characteristics of patients with thyrotoxicosis, categorized by Tc-99m thyroid uptake level and final diagnosis

Variable	Tc-99m uptake ≥ 1%					
Final diagnosis	Graves' disease	Spontaneously remitted Graves' disease	Atypical Graves' disease	Graves' disease + subacute thyroiditis	Autonomously functioning thyroid nodule	Others
Case number[a]	—	1 - 4	5	6	—	7
n (%)	263 (76.7)					
	255 (74.3)	4 (1.2)	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Age (years)	49 ± 15	56 ± 15	75	62	49	19
Gender (male/female)	54/201	0/4	1/0	1/0	0/1	0/1
Tc-99m uptake (%)	6.6 [1.0 - 42.5]	2.0 [1.9 - 4.0]	1.0	1.1	1.8	1.5
TSH (μIU/mL)	< 0.10	< 0.10	< 0.10	< 0.10	< 0.10	< 0.10
FT3 (pg/mL)	12.68 ± 8.35	3.89 ± 0.61	4.21	10.31	4.39	3.08
FT4 (ng/dL)	2.90 ± 1.15	1.67 ± 0.54	1.88	4.60	1.33	1.62
FT3/FT4 ratio	4.14 ± 1.80	2.46 ± 0.59	2.24	2.24	3.30	1.9
TBII (IU/L)	8.5 [0.0 - 231.2]	2.1 [0.0 - 16.2]	1.6	8.7	1.0	< 1.0
TBII (+), *n* (%)	243 (95.3)	3 (75.0)	1 (100.0)	1 (100.0)	1 (100.0)	0 (0.0)
TSAb (%)	508 [79 - 5,464]	134 [100 - 512]	176	600	151	164
TSAb (+), *n* (%)	219 (85.9)	2 (50.0)	0 (0.0)	1 (100.0)	1 (100.0)	0 (0.0)
TPOAb (IU/mL)	92.8 [0.0 - 600.0]	8.8 [6.3 - 326.8]	421.1	18.0	6.0	5.2
TPOAb (+), *n* (%)	170 (66.7)	1 (25.0)	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)
TgAb (IU/mL)	116.2 [0.0 - 4,000.0]	249.4 [15.1 - 3,969.0]	18.0	18.8	15.6	17.4
TgAb (+), *n* (%)	163 (63.9)	3 (75.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Variable	Tc-99m uptake ≥ 0.5%/< 1%					
Final diagnosis	Graves' disease	Atypical Graves' disease	Subclinical Graves' disease	Painless thyroiditis	Autonomously functioning thyroid nodule	Unknown
Case number[a]	8 - 14	15	16	17	—	18
n (%)	13 (3.8)					
	7 (2.0)	1 (0.3)	1 (0.3)	1 (0.3)	2 (0.6)	1 (0.3)
Age (Years)	60 ± 17	54	33	41	49 ± 1	66
Gender (Male/Female)	2/5	0/1	0/1	1/0	0/2	0/1
Tc-99m uptake (%)	0.8 [0.5 - 0.9]	0.6	0.6	0.8	0.7 [0.5 - 0.8]	0.9
TSH (μIU/mL)	< 0.10	< 0.10	< 0.10	< 0.10	< 0.10	< 0.10
FT3 (pg/mL)	7.30 ± 5.77	6.80	2.21	3.19	4.82 ± 3.76	6.64
FT4 (ng/dL)	2.59 ± 1.30	2.68	0.91	1.11	1.89 ± 1.01	1.90
FT3/FT4 ratio	2.67 ± 0.73	2.54	2.43	2.87	2.36 ± 0.73	3.49
TBII (IU/L)	6.1 [0.0 - 37.3]	2.0	3.2	< 1.0	0.6 [0.0 - 1.1]	< 1.0
TBII (+), *n* (%)	6 (85.7)	1 (100.0)	1 (100.0)	0 (0.0)	1 (50.0)	0 (0.0)
TSAb (%)	310 [98 - 954]	305	526	95	131 [131 - 131]	107
TSAb (+), *n* (%)	5 (71.4)	1 (100.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)
TPOAb (IU/mL)	10.8 [0.0 - 270.3]	9.3	31.4	120.1	33.4 [6.4 - 60.3]	N/A
TPOAb (+), *n* (%)	3 (42.9)	0 (0.0)	1 (100.0)	1 (100.0)	1 (50.0)	N/A
TgAb (IU/mL)	33.2 [0.0 - 709.4]	11.0	11.3	583.1	14.6 [10.3 - 18.9]	N/A
TgAb (+), *n* (%)	4 (57.1)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	N/A

Table 1 Biochemical characteristics of patients with thyrotoxicosis, categorized by Tc-99m thyroid uptake level and final diagnosis (continued)

Variable	Tc-99m uptake < 0.5%				
Final diagnosis	Painless thyroiditis	Subacute thyroiditis	Autonomously functioning thyroid nodule	Others	Unknown
Case number[a]	—	—	—	19 - 21	22
n (%)	67 (19.5)				
	33 (9.6)	29 (8.5)	1 (0.3)	3 (0.9)	1 (0.3)
Age (Years)	49 ± 18	50 ± 11	59	60 ± 8	58
Gender (Male/Female)	13/20	6/23	0/1	2/1	0/1
Tc-99m uptake (%)	0.1 [0.1 - 0.4]	0.1 [0.0 - 0.3]	0.2	0.1 [0.1 - 0.2]	0.3
TSH (μIU/mL)	< 0.10	< 0.10	< 0.10	< 0.10	< 0.10
FT3 (pg/mL)	5.30 ± 3.29	5.86 ± 2.53	3.44	3.44 ± 1.12	2.96
FT4 (ng/dL)	1.84 ± 0.64	2.50 ± 0.68	1.66	1.91 ± 0.10	1.27
FT3/FT4 ratio	2.74 ± 0.75	2.32 ± 0.53	2.07	1.80 ± 0.61	2.33
TBII (IU/L)	0.0 [0.0 - 5.1]	0.0 [0.0 - 99.3]	< 1.0	0.0 [0.0 - 0.0]	< 1.0
TBII (+), *n* (%)	9 (28.1)	4 (13.8)	0 (0.0)	0 (0.0)	0 (0.0)
TSAb (%)	116 [75 - 390]	120 [77 - 212]	153	87 [79 - 141]	115
TSAb (+), *n* (%)	9 (28.1)	6 (21.4)	0 (0.0)	0 (0.0)	0 (0.0)
TPOAb (IU/mL)	14.4 [0.0 - 600.0]	8.5 [0.0 - 33.7]	227.5	0.0 [0.0 - 10.5]	5.4
TPOAb (+), *n* (%)	13 (40.6)	3 (10.3)	1 (100.0)	0 (0.0)	0 (0.0)
TgAb (IU/mL)	174.5 [0.0 - 756.3]	20.7 [0.0 - 503.4]	507.9	14.5 [13.8 - 84.9]	< 10.0
TgAb (+), *n* (%)	18 (58.1)	13 (44.8)	1 (100.0)	1 (33.3)	0 (0.0)

All data were obtained at the time of initial diagnosis.

[a] The case numbers denote those listed in Tables 2a and 2b summarizing patient biochemical characteristics and clinical course.

N/A: not available. Data are expressed as mean ± SD, median [min - max], or number.

Reference ranges: TSH, 0.49-4.67 or 0.35-4.94 μIU/mL; FT3, 1.45-3.48 or 1.71-3.71 pg/mL; FT4, 0.71-1.85 or 0.70-1.48 ng/dL; TBII < 1.0 IU/L; TSAb < 180% or ≤ 120%; TPOAb, < 16.0 IU/mL; and TgAb, < 28.0 IU/mL

TcTU test to differentiate Graves' disease from thyroiditis[25–27]. However, no laboratory test is definitive in differentiating Graves' disease from painless thyroiditis.

T3/T4 ratio is reported to be higher in patients with Graves' disease, in part because type II deiodinase, which is abundantly expressed in human thyroid tissue[28], is stimulated by TSH receptor-stimulating antibodies[29], thus promoting the use of T3/T4 ratio for differential diagnosis of Graves' disease and painless thyroiditis. In 1 report, serum T3/T4 ratio was higher than 20 in 14 patients with Graves' disease but lower than 20 in all patients with painless thyroiditis[30]. In another study, 85.5% of thyrotoxic patients with a T3/T4 ratio of >20 had Graves' disease, while some patients with painless thyroiditis also had a T3/T4 ratio of >20[31]. Therefore, although T3/T4 ratio helps differentiate Graves' disease from painless thyroiditis, it is not sufficient to differentiate these conditions.

Some studies have investigated ultrasonography-based differential diagnosis of Graves' disease and painless thyroiditis. Bogazzi et al. reported that a thyroid blood flow >4% differentiated Graves' disease from destruction-induced thyrotoxicosis[32]. Zuhur et al.[13] reported that a cut-off value of 30 cm/s for mean inferior thyroid artery peak systolic velocity (ITA-PSV) and 13.2 cm/s for end diastolic velocity had a sensitivity/specificity of 95.3%/94.9% and 89.3%/88.6%, respectively, in discriminating Graves' disease from silent thyroiditis. Using a mean ITA-PSV cut-off value of 30 cm/s, Malik et al.[26] reported that mean ITA-PSV values were significantly higher for patients with Graves' disease than for those with thyroiditis (sensitivity, 91%; specificity, 89%). Thus, although ultrasonography may help differentiate Graves' disease from painless thyroiditis, it is not sufficient for that purpose.

Graves' disease is thought to be an autoimmune disease caused by TBII, and TBII positivity is a likely hallmark of Graves' disease[33]. Sayama et al.[34] reported that 31 of 37 patients with Graves' disease (84%) were positive for TBII, as measured by a TSH receptor assay kit (RSR

Table 2a Detailed biochemical characteristics of patients with an atypical clinical course or ambiguous initial diagnosis

Variable	Tc-99m uptake ≥1%						
Final diagnosis	Spontaneously remitted Graves' disease				Atypical Graves' disease	Graves' disease + subacute thyroiditis	Others
Case number	1	2	3	4	5	6	7
Age (years)	59	50	40	75	75	62	19
Gender (male/female)	female	female	female	female	male	male	female
Tc-99m uptake (%)	2.0	4.0	1.9	1.9	1.0	1.1	1.5
TSH (μIU/mL)	< 0.10[a]	< 0.10[a]	< 0.10[b]	< 0.10[b]	< 0.10[a]	< 0.10[a]	< 0.10[a]
FT3 (pg/mL)	3.53[a]*	3.97[a]*	3.35[b]	4.71[b]*	4.21[a]*	10.31[a]*	3.08[a]
FT4 (ng/dL)	1.43[a]	2.44[a]*	1.21[b]	1.59[b]*	1.88[a]*	4.60[a]*	1.62[a]
FT3/FT4 ratio	2.47	1.63	2.77	2.96	2.24	2.24	1.90
TBII (IU/L)	1.9*	16.2*	2.2*	< 1.0	1.6*	8.7*	< 1.0
TSAb (%)	100[a]	512[a]*	147[b]*	120[b]	176[a]	600[a]*	164[a]
TPOAb (IU/mL)	10.5	326.8*	6.3	7.0	421.1*	18.0*	5.2
TgAb (IU/mL)	132.7*	3,969*	15.1	366.0*	18.0	18.8	17.4

Variable	Tc-99m uptake ≥0.5%/< 1%										
Final diagnosis	Graves' disease							Atypical Graves' disease	Sub-clinical Graves' disease	Painless thyroiditis	Unknown
Case number	8	9	10	11	12	13	14	15	16	17	18
Age (Years)	74	74	38	47	73	43	74	54	33	41	66
Sex (Male/Female)	Female	Male	Female	Female	Male	Female	Female	Female	Female	male	female
Tc-99m uptake (%)	0.9	0.5	0.8	0.8	0.8	0.7	0.5	0.6	0.6	0.8	0.9
TSH (μIU/mL)	< 0.10[a]	< 0.10[a]	< 0.10[a]	< 0.10[b]	< 0.10[b]	< 0.10[b]	< 0.10[b]	< 0.10[a]	< 0.10[b]	< 0.10[b]	< 0.10[b]
FT3 (pg/mL)	6.87[a]*	5.02[a]*	20.10[a]*	6.28[b]*	5.33[b]*	4.10[b]*	3.41[b]	6.80[a]*	2.21[b]	3.19[b]	6.64[b]*
FT4 (ng/dL)	2.67[a]*	3.04[a]*	5.27[a]*	1.89[b]*	1.86[b]*	1.79[b]*	1.58[b]*	2.68[a]*	0.91[b]	1.11[b]	1.90[b]*
FT3/FT4 ratio	2.57	1.65	3.81	3.32	2.87	2.29	2.16	2.54	2.43	2.87	3.49
TBII (IU/L)	7.3*	3.9*	37.3*	7.5*	6.1*	< 1.0	4.1*	2.0*	3.2*	< 1.0	< 1.0
TSAb (%)	954[a]*	310[a]*	567[a]*	147[a]	547[a]*	98[b]	308[b]*	305[a]*	526[b]*	95[b]	107[a]
TPOAb (IU/mL)	< 5.0	< 5.0	270.3*	135.8*	10.8	9.2	155.1*	9.3	31.4*	120.1*	N/A
TgAb (IU/mL)	< 10.0	709.4*	33.2*	172.7*	10.5	< 10.0	344.9*	11.0	11.3	583.1*	N/A

Variable	Tc-99m uptake < 0.5%			
Final diagnosis	Others			Unknown
Case number	19	20	21	22
Age (Years)	68	52	60	58
Sex (Male/Female)	Female	Male	Male	Female
Tc-99m uptake (%)	0.2	0.1	0.1	0.3
TSH (μIU/mL)	< 0.10[b]	< 0.10[b]	< 0.10[b]	< 0.10[b]
FT3 (pg/mL)	2.80[b]	4.73[b]*	2.78[b]	2.96[b]
FT4 (ng/dL)	2.02[b]*	1.89[b]*	1.83[b]*	1.27[b]
FT3/FT4 ratio	1.39	2.50	1.52	2.33
TBII (IU/L)	< 1.0	< 1.0	< 1.0	< 1.0
TSAb (%)	141[a]	79[a]	87[b]	115[b]
TPOAb (IU/mL)	< 5.0	10.5	< 5.0	5.4
TgAb (IU/mL)	14.5	84.9*	13.8	< 10.0

N/A, not available. Data are expressed as numbers.

Reference ranges: TSH, [a] 0.49-4.67 or [b] 0.35-4.94 μIU/mL; FT3, [a] 1.45-3.48 or [b] 1.71-3.71 pg/mL; FT4, [a] 0.71-1.85 or [b] 0.70-1.48 ng/dL; TBII, < 1.0 IU/L; TSAb, [a] < 180% or [b] ≤120%; TPOAb, < 16.0 IU/mL; and TgAb, < 28.0 IU/mL. Non-marked values indicate those within the reference range; asterisks indicate values above the reference range.

Table 2b Summary of patients with an atypical clinical course or ambiguous initial diagnosis

Case number	Clinical course
1	A euthyroid state was attained without treatment within 3 months, and the patient remained in a euthyroid state for another month, and follow-up was stopped.
2	A euthyroid state was attained without treatment within 3 months and the patient was in a euthyroid state at 11 months.
3	A euthyroid state was attained without treatment 4 months later, and TSH was below detectable levels and FT3 and FT4 levels remained in normal range at 10 months. TSH returned to normal at 17 months without treatment.
4	A euthyroid state was attained within 3 months and the patient remained in a euthyroid state for another 4 months.
5	FT3, FT4 were elevated at the initial diagnosis, but they spontaneously returned to within normal range after about 3 weeks, and TSH continued to be undetectable. Seven months later, the patient developed overt thyrotoxicosis and was started on treatment with methimazole.
6	Graves' disease and subacute thyroiditis simultaneously occurred. A diagnosis of subacute thyroiditis was confirmed by cytology.
7	The patient was found to be pregnant.
8	Thyrotoxicosis with high TSAb titer complicated by congestive heart failure due to dilated cardiomyopathy. Immediately after the TcTU test, the patient was started on methimazole 15 mg. With thyroid functions rapidly normalized, the patient developed hypothyroidism at two months. With the methimazole dose decreased to 5 mg, thyrotoxicosis never relapsed thereafter, suggesting painless thyroiditis, given the very rapid effect obtained with methimazole.
9	Angina pectoris complicated by thyrotoxicosis. The low TcTU value suggested painless thyroiditis and high TSAb titer suggested Graves' disease. With KI treatment, thyroid function normalized, but thyrotoxicosis relapsed 4 months later when the dose of KI was decreased, and the patient was started on treatment with methimazole.
10	Thyroid function was normalized with methimazole treatment. During the treatment, serum TSH fell below detectable levels at 6 months.
11	Observation was deemed the treatment of choice due to a low TcTU value and negativity for TSAb. With thyrotoxicosis worsening, the patient was started on treatment with methimazole one month later.
12	TSH was below detectable levels 6 months after starting methimazole.
13	A low TcTU value and negativity for TSAb suggested painless thyroiditis, but thyrotoxicosis persisted for more than 10 months and the patient was started on treatment with methimazole.
14	A low TcTU value was noted but hyperthyroxinemia persisted for three months, and the patient was lost to follow-up thereafter.
15	A high TSAb titer and spontaneously resolving thyrotoxicosis were noted. While the TSAb titer was decreased to a level suggesting TSAb negativity, thyrotoxicosis and TSAb positivity relapsed 15 months later.
16	A high TSAb titer and TSH below detectable levels were noted, but FT3 and FT4 were within normal range. While TSH continued to be below detectable levels, the patient progressed to overt thyrotoxicosis five months later, and was started on treatment with propylthiouracil.
17	A euthyroid state was observed two weeks later, leading to the diagnosis of painless thyroiditis in the patient.
18	Levothyroxine 12.5 μg had been administered until two weeks before the TcTU test. Thyroid functions were normalized after stopping levothyroxine for 4 weeks. Exogenous thyroid hormone was suspected but it remained unclear why the TcTU value was not very low.
19	The patient was found to have had an overdose of levothyroxine.
20	The patient was found to have amiodarone-induced thyroid disorder.
21	The patient was found to have amiodarone-induced thyroid disorder.
22	For several years, serum TSH were shown to fall below detectable levels and return to normal levels by turns. Exogenous thyroid hormone was suspected but unproved.

Ltd., Pentwyn, Cardiff, UK). Another report found that 64 of 67 of patients with Graves' disease (96%) were positive for TBII, as measured by a radioreceptor assay using the DYNOtest TRAb Human kit Yamasa (Yamasa, Chiba, Japan)[35]. As shown in **Table 1**, more than 95% of the present patients with Graves' disease were positive for TBII, which is consistent with these earlier reports. In addition, more than 90% of patients with untreated Graves' disease were positive for TSAb in previous studies[36,37], while nearly 90% of the present patients were positive for TSAb. In other words, these data suggest that TSH-receptor antibody status is not sufficient to establish a diagnosis of Graves' disease.

Painless thyroiditis is also considered to be an autoimmune disease and is common in patients with chronic thyroiditis; however, its causes are unclear[24]. In fact, some patients were negative for both TPOAb and TgAb (10 of 34; 29%) in this study. However, despite the large proportion of patients who were negative for both antibodies, we cannot exclude the possibility that false-negative results were a consequence of the measurement sensitivity of the test[38] and that patients with no chronic thyroiditis may have developed painless thyroiditis[24,39]. Therefore, it may not be easy to accurately diagnose painless thyroidi-

tis at the initial visit. In contrast, more than 25% of patients with painless thyroiditis (9/34) were TBII-positive in the present study, a higher proportion than in earlier studies, which reported TBII positivity in approximately 0-15% of patients with transient thyrotoxicosis or painless thyroiditis[14,34,40], although patient characteristics and TBII measurement methods differed. In addition, Sanyal et al.[41] reported that, given that 22.4% of patients with painless thyroiditis were TRAb-positive, diagnosis of painless thyroiditis could not be reliably confirmed using TRAb assays. Similarly, more than 25% (9/34) of patients with painless thyroiditis were positive for TSAb in the present study. Thus, if Graves' disease had been diagnosed on the basis of TBII or TSAb results, up to one quarter of patients with painless thyroiditis might have been diagnosed with and treated for Graves' disease. That appears to be a pitfall in diagnosing Graves' disease in clinical practice, given that it remains difficult to determine whether patients with TBII-positive or TSAb-positive hyperthyroidism have Graves' disease.

There are a small but non-negligible number of patients whose diagnosis remain in question even after undergoing various diagnostic tests. In the present study, 4 patients (1%) with Graves' disease experienced spontaneous remission, ie, thyroid function normalized spontaneously without treatment within 3 months because symptoms were mild or for other reasons. No obvious trend was identified in the characteristics of these patients (**Table 2a**), suggesting that clinical data at initial diagnosis are insufficient to predict spontaneous remission of Graves' disease. Furthermore, the clinical course of self-remitting Graves' disease closely resembled that of painless thyroiditis, except for the absence of a hypothyroid phase. Therefore, many more patients may have experienced spontaneous remission of Graves' disease. We are developing a method to investigate this that allows for ethically acceptable patient follow-up.

As mentioned above, the main purpose of distinguishing between Graves' disease and painless thyroiditis is to determine a treatment plan, that is, to avoid unnecessary treatment. From this point of view, diseases in which the need for immediate treatment can be obviated, such as painless thyroiditis with or without Hashimoto thyroiditis; spontaneously remitting, subclinical, and fluctuating Graves' disease; and other thyroid diseases of unknown mechanisms, it may be advisable to withhold diagnosis as the tentative diagnosis. The observation period for the present patients ranged from 1 to 54 months, and no adverse effects were attributed to inability to confirm the diagnosis at the initial visit and start treatment immediately. In patients with hyperthyroidism symptoms that are mild and tolerable, observation without treatment may thus be warranted.

Graves' disease, Hashimoto thyroiditis, and painless thyroiditis are all categorized as autoimmune thyroid diseases. Several case studies reported that Graves' thyrotoxicosis transitioned to Hashimoto hypothyroidism and vice versa[42–44], suggesting that Graves' disease may be a dynamic disease that presents with various phenotypes at different time points. Perhaps Graves' disease, Hashimoto thyroiditis, and painless thyroiditis are phases of the same autoimmune thyroid disease, and thus may be difficult to differentiate in some patients.

We analyzed the frequency of hyperthyroidism causes. Of the 343 patients, 262 (76%) had Graves' disease, 34 (10%) had painless thyroiditis, and 29 (8%) had subacute thyroiditis. Given that Graves' disease, transient hyperthyroidism, and subacute thyroiditis were reported to account for 76%, 14.7%, and 9.3% of all cases of thyrotoxicosis, respectively[17], the frequencies of Graves' disease, painless thyroiditis, and subacute thyroiditis as causative diseases of hyperthyroidism reported in this study are comparable to those in previous reports. However, because the study data were collected before the advent of immune check point inhibitors, which led to exclusion of irAE thyroid diseases such as new-onset destructive thyroiditis or Graves' disease after initiating treatment with immune checkpoint inhibitors[45–48], they are currently being evaluated for their clinical course at our hospital.

The present study has several limitations. First, single-center-verified diagnoses may result in selection bias. Therefore, a future multicenter study should attempt to verify whether similar results can be obtained across multiple centers. Second, the sample size was small, which might have affected the study results. Therefore, it is necessary to verify if similar results can be obtained in large-scale clinical trials. Finally, changes in measuring equipment for some of the present clinical variables may have affected the results.

In conclusion, the question "Graves' disease or not?" differs from the question "malignant or not?", as Graves' disease is a dynamic disease with ever-changing characteristics. It may be time to reconsider the current paradigm in which painless thyroiditis and Graves' disease are assumed to represent distinct disease entities. The present results suggest that only a retrospective evaluation can definitively diagnose Graves' disease. Spontaneously remitting, subclinical, and fluctuating Graves'

disease, as well as painless thyroiditis, may not ultimately lend themselves to differential diagnosis. Physicians must consider this and understand that careful follow up of these diseases after a tentative diagnosis may represent better care for patients with hyperthyroidism. This is the first report clearly demonstrating that so far there is no gold standard for the diagnosis of Graves' disease. A consensus on the definition of Graves' disease is urgently needed. Without such a consensus, we cannot determine the specificity and sensitivity of future diagnostic tests.

Data Availability: Some or all the data sets generated during the present study are not publicly available but are available on reasonable request through the corresponding author.

Author Contributions: All authors made a significant contribution to the work, including the conception, study design, acquisition, analysis, and interpretation of data, and writing, review, and editing of the manuscript.

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