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Unexplained Hyperthyroglobulinemia in Differentiated Thyroid Cancer Patients Indicates Radioiodine Adjuvant Therapy: A Prospective Multicenter Study

Lin Cheng[1*], Ri Sa[1*], Qiong Luo[2*], Hao Fu[1], Yuchen Jin[1], Linglin Tang[3], Yi Yang[4], Chunjing Yu[5], and Libo Chen[1]

[1]Department of Nuclear Medicine, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, 600 Yishan Road, Shanghai 200233, China

[2]Department of Nuclear Medicine, Tenth People's Hospital of Tongji University, 301 Yanchang Middle Road, Shanghai 200072, China

[3]Department of Nuclear Medicine, Ren Ji Hospital, Shanghai Jiao Tong University, School of Medicine, 160 Pujian Road, Shanghai 200127, China

[4]Department of Nuclear Medicine, The Affiliated Suzhou Science & Technology Town Hospital of Nanjing Medical University, 1 Lijiang Road, Suzhou, Jiangsu 215153, China

[5]Department of Nuclear Medicine, Affiliated Hospital of Jiangnan University, 200 Huihe Road, Wuxi, Jiangsu 214062, China

[*]Lin Cheng, Ri Sa, and Qiong Luo were the co-first authors.

Contact information for first author:

Lin Cheng (student)

600 Yishan Rd, Shanghai 200233, China

Tel: +86-18017317895; Fax: +86-21-64941720

E-mail: chenglin0321@sjtu.edu.cn

Contact information for correspondence:

Libo Chen

600 Yishan Rd, Shanghai 200233, China

Telephone: +86-21-24058871; Fax: +86-21-64941720

E-mail: lbchen@sjtu.edu.cn

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Abstract

Background: The management for totally thyroidectomized differentiated thyroid cancer (TT-DTC) patients with unexplained hyperthyroglobulinemia remains indeterminate due to evidence scarcity. This multicenter study aimed at prospectively evaluating the response to radioiodine (^{131}I) adjuvant therapy (RAT) and its potential role in risk stratification and causal clarification.

Methods: TT-DTC patients with stimulated serum thyroglobulin (Tg_{off}) levels > 10 ng/mL but no structurally evident disease were consecutively enrolled in five tertiary care institutions. After the administration of 5.55 GBq of ^{131}I, the risk of presence of persistent/recurrent/metastatic DTC (prmDTC) was compared to that before RAT. The causes of hyperthyroglobulinemia were explored and the response to RAT was assessed 6-12 months post RAT. The change in suppressed thyroglobulin (Tg_{on}) level was reported.

Results: A cohort of 254 subjects with a median Tg_{off} of 27.1 ng/mL was enrolled for the analyses. Immediately after RAT, low-, intermediate-, and high-risk were identified in 5.9%, 88.6%, and 5.5% patients, respectively, with no significant difference in risk stratification compared with that before RAT (p = 0.952). During the follow-up (median, 10.6 months), hyperthyroglobulinemia was ultimately attributed to thyroid remnant, biochemical disease, and structural/functional disease in 17.3%, 54.3%, and 28.3% of subjects, respectively. In addition, excellent, indeterminate, biochemical incomplete, and structural/functional incomplete responses were achieved in 18.1%, 27.2%, 36.2%, and

18.5% of patients, respectively. Notably, distribution for either cause of hyperthyroglobulinemia or response to RAT was comparable among the three postoperative risk groups. Tg_{on} levels in patients who merely received RAT declined significantly over time.

Conclusions: Our study demonstrated that over 90% of TT-DTC patients with unexplained hyperthyroglobulinemia are stratified as intermediate-high risk, and RAT using 5.55 GBq of ^{131}I reveals biochemical/functional/structural disease and yields non-structural/functional incomplete response in more than 80% patients, suggesting TT-DTC patients with unexplained hyperthyroglobulinemia as explicit candidates for RAT.

INTRODUCTION

With the exception of active surveillance and thermal ablation in patients with low-risk microscopic papillary thyroid cancer, the initial management of differentiated thyroid cancer (DTC) mainly relies on surgery followed by radioiodine (^{131}I) remnant ablation (RRA), radioiodine adjuvant therapy (RAT) of potential residual thyroid cancer, or radioiodine treatment (RT) of known disease, under thyroid-stimulating hormone (TSH) suppression (*1-3*).

Before ^{131}I administration, the postoperative serum thyroglobulin (Tg) level measured either at the stimulated (Tg_{off}) or suppressed (Tg_{on}) TSH level is of great value in both disease monitoring and management decision making, since hyerthyroglobulinemia a few weeks after total thyroidectomy is highly associated with persistent/recurrent/metastatic DTC (prmDTC) and survival (*4-8*). The 2015 American Thyroid Association (ATA) guidelines pointed out that patients with postoperative Tg_{off} values > 10 ng/mL will likely need additional evaluations and possibly even complementary therapies (*1*). Unfortunately, although it has been over 10 years since the term “thyroglobulinemia” was initially raised by the well acknowledged 2009 ATA guidelines (*9*), few dedicated data can be referred on totally thyroidectomized DTC (TT-DTC) patients with unexplained hyperthyroglobulinemia, partially due to the interference of patients with structural disease in previous studies (*7,10*). Consequently, the relationship between hyperthyroglobulinemia and risk of carrying prmDTC, the primary cause of unexplained hyperthyroglobulinemia,

and the response to ^{131}I administration in such patients remain largely unknown.

Aiming at facilitating initial staging and follow-up, improving disease-specific survival and progression-free survival, and decreasing recurrence, RAT should be considered or routinely recommended in intermediate-risk or high-risk patients, respectively, but not in low-risk patients, with regard to guidelines issued by the ATA (*1*). However, the implication of serum Tg level in the risk stratification is not fully clarified and the attempt in the definition/indication of RAT is retarded, since the precise cut-off value of Tg in distinguishing neither intermediate- from low- or high-risk patients nor RAT form RRA or RT has been firmly established. Hence, we conducted this prospective multicenter study to assess the response to RAT and its potential role in risk stratification and causal clarification in a dedicated cohort of TT-DTC patients with unexplained hyperthyroglobulinemia regardless of postoperative risk stratification, in order to establish a potential indication for RAT.

METHODS

Patients

TT-DTC patients with hyperthyroglobulinemia, whose Tg_{off} levels at more than 4 weeks after total thyroidectomy and just before RAT were > 10 ng/mL, were consecutively recruited from June 2009 in five tertiary care institutions. Patients with prmDTC lesion identified by neck ultrasonography (US) (*1*), chest CT, ^{99m}Tc-methylene diphosphonate whole-body scan, magnetic resonance imaging, or ^{18}F-fluorodeoxyglucose positron-

emission tomography/CT (^{18}F-FDG-PET/CT) were excluded. Consequently, Tg_{off} over 10 ng/mL in TT-DTC patients without structurally evident prmDTC was defined as unexplained hyperthyroglobulinemia and comprehensively analyzed.

Just before RAT, patients with radioiodine uptake (RAIU) >15% were excluded to ensure the success in RRA as previously described by our group (*11*). Serum TSH, Tg, and anti-Tg antibody (TgAb) levels were measured by electrochemiluminescence immunoassay on a Cobas analyzer (Roche Diagnostics Gmbh, Roche Ltd., Basel, Switzerland). The upper detection limit of the TSH assay was 100 mIU/L, and TSH levels higher than that were counted as 100 mIU/L. Similarly, Tg and TgAb levels lower than their thresholds were counted as 0.04 ng/mL and 10 IU/mL, respectively. Neck US and chest CT were conducted in all patients before RAT.

For RAT, an activity of 5.55 GBq of ^{131}I was orally administered. Three days later, a planar whole-body scan was performed with SPECT/CT if needed (*12*). RT was performed 6 months after RAT in patients if ^{131}I-avid prmDTC lesions were identified by post RAT scan; conversely, patients without overt structural/functional disease were regularly followed up for more than one year under TSH suppression. The examinations of Tg_{on} and neck US were conducted at each follow-up visit. The follow-up visit and possible modulation of levothyroxine dosage were conducted at 1, 4, and 12 months post RAT except as otherwise indicated, then the interval was extended to 6-12 months. The assessment of therapeutic response to RAT and primary cause of hyperthyroglobulinemia

were revealed 6-12 months post RAT.

The institutional review boards approved this study and all subjects signed a written informed consent.

Risk stratification

According to the 2009 ATA guidelines, the three-tiered system, including low-, intermediate-, and high-risk of presence of prmDTC was utilized with minor revisions (*9*). Low-risk patients were characterized by intrathyroidal DTC with no evidence of extrathyroidal extension, vascular invasion, aggressive histology or metastases. Intermediate-risk patients were featured by either microscopic extrathyroidal extension, cervical lymph node metastases, ^{131}I-avid disease in the neck outside the thyroid bed, vascular invasion, or aggressive tumor histology. High-risk patients were distinguished by either gross extrathyroidal extension, incomplete tumor resection, or distant metastases.

Causal categorization

The primary causes of postoperative unexplained hyperthyroglobulinemia were revealed based on the findings of post RAT scan, consecutive serum Tg tests, medical imaging, US-guided fine needle aspiration in combination with pathological examination, and correlation with clinical follow-up within 6 to 12 months post RAT.

Thyroid remnant was determined based on visible uptake in the normal thyroid bed or ectopia on post RAT scan, absence of prmDTC, and Tg_{on} level < 0.2 ng/mL. Biochemical disease was affirmed by the absence of structural/functional evidence of prmDTC but Tg_{on}

level ≥ 0.2 ng/mL. Structural/functional disease was defined as any evidence of prmDTC lesions identified by post RAT scan and/or other imaging examinations during surveillance.

Response to RAT

According to the 2015 ATA guidelines, a response evaluation scheme with four categories was adopted with minor modifications 6-12 months post RAT (*1*). The definitions of excellent response (ER), indeterminate response (IR) and biochemical incomplete response (BIR) remained. Structural/functional incomplete response (S/FIR) endorsed positive anatomic/metabolic imaging evidence of disease with any Tg level. IR, BIR and SIR were collectively assigned as non-ER, while ER, IR and BIR were grouped as non-S/FIR.

Statistical analyses

All analyses were conducted using SPSS (version 20) software. Continuous data are presented as the means with standard deviations or medians with interquartile ranges for normal and abnormal distribution, respectively. Categorical variables are displayed as number with percentage. Comparison in categorical variable was performed using χ^2 test or Fisher's exact test. Variance analysis was applied for continuous data with normal distribution. The predictive value of Tg_{off} for primary cause of hyperthyroglobulinemia was evaluated by univariate receiver operating characteristics analysis in combination with DeLong test for comparing the area under the curve (AUC). Wilcoxon signed-rank test for Tg level was performed at multiple time points. Two-tailed probabilities were reported, and

a p value < 0.05 was considered statistically significant.

RESULTS

Baseline characteristics

From June 2009 through August 2018, a total of 469 TT-DTC patients with Tg_{off} >10 ng/mL were enrolled. After the exclusion of 215 patients (8 patients with TgAb > 100 IU/mL, 55 patients with RAIU > 15%, 114 patients with suspicious cervical loco-regional disease, and 38 patients with possible distant metastases), 54.2% (254/469) of patients deemed as having unexplained hyperthyroglobulinemia were eligible for further analyses.

The baseline characteristics of the 254 subjects are summarized in Table 1. The mean age at diagnosis was 38.3 ± 11.8 years, with a male-to-female ratio of 1:1.65. A total of 252 (99.2%) patients were classified as stage I or II. None of the enrolled patients had undergone RRA before RAT. The mean interval between surgery and RAT was 4.2 ± 3.3 months. The postoperative median Tg_{on} was 3.7 ng/mL, which increased up to 27.1 ng/mL just before RAT, when a median TSH level was 100 mIU/mL at 4 weeks after thyroid hormone withdrawal.

Risk stratification

In the postoperative risk stratification, only 17 (6.7%) of the 254 eligible patients were categorized into the low-risk group. A total of 225 (88.6%) and 12 (4.7%) patients were classified as having intermediate- and high-risk of harboring prmDTC, respectively. Once post-RAT scan findings were obtained, 11.8% (2/17) of postoperative low-risk patients

switched to the intermediate-risk group for the identification of nodule disease, replacing another two intermediate-risk patients who were transferred to the high-risk group because of distant metastasis. Thus, the number of patients with intermediate-risk remained at 225. No significant difference in the risk distribution between the two time points (before and after RAT) was achieved ($p = 0.952$) (Fig. 1).

Causal categorization

According to the findings in a median follow up of 10.6 months (range, 7.3-13.8 months), the unexplained postoperative hyperthyroglobulinemia could be ultimately attributed to thyroid remnant in 17.3% (Fig. 2), biochemical disease in 54.3%, and structural/functional disease in 28.4% (Figs. 3 and 4) of the 254 patients (Fig. 5).

The causal classification regarding the postoperative risk of the presence of prmDTC is shown in Table 2. Again, no significant difference in causal proportion was achieved among the three risk groups ($p = 0.526$). Moreover, the proportion of either biochemical or structural/functional disease in the intermediate-high risk group was comparable with that in the low-risk group ($p = 0.465$).

Furthermore, the comparisons of factors potentially associated with the cause of unexplained hyperthyroglobulinemia in TT-DTC patients are shown in Table 3. The median Tg_{off} level significantly differed among the three casual groups ($p = 0.000$). The cut-off value of Tg_{off} for distinguishing thyroid remnant from biochemical/structural/functional disease was 19.5 ng/mL, with an AUC of 0.714, a sensitivity of 68.2%, and a specificity of

70.0% ($p < 0.0001$). In addition, a Tg_{off} level of 27.9 ng/mL was obtained as the cut-off value isolating structural/functional disease from thyroid remnant and biochemical disease with an AUC of 0.630, a sensitivity of 68.2%, and a specificity of 58.8% ($p = 0.0009$). However, no significant difference in RAIU, TSH or TgAb value was achieved among the three causal groups with a comparable proportion of patients with TSH > 100 mIU/mL or TgAb < 10 IU/mL.

Of the 72 patients causally attributed to structural/functional disease, 38 (52.8%) patients received RT due to the ^{131}I-avidity of prmDTCs demonstrated by post RAT scan, in which 1, 2, and 3 courses of RT were given in 33 (86.8%) , 3 (7.9%), and 2 (5.3%) patients, respectively. Thirty-four patients were identified with prmDTC during the 6-12 months follow-up, in which, three underwent cervical lymph node resection, and the remaining 31 (43.1%) patients were under active surveillance with TSH suppression.

Additionally, two patients with anatomically negative but functionally positive disease were identified. One with pulmonary metastases achieved negative ^{131}I- whole-body scan after the second therapeutic dose, and the other with iliac metastasis, who received RT followed by bone lesion resection, obtained a disease-free status in the subsequent 1-year follow-up.

Response to RAT

Overall, 46 (18.1%), 69 (27.2%), 92 (36.2%), and 47 (18.5%) of the 254 eligible patients achieved ER, IR, BIR, and S/FIR, respectively (Fig. 5).

Regarding postoperative risk stratification, ER was achieved in 35.3% (6/17) low-risk patients, 16.4% (37/225) intermediate-risk patients, and 25.0% (3/12) high-risk patients (p = 0.119). Besides, S/FIR was obtained in 11.8% (2/17) low-risk patients, 19.6% (44/225) intermediate-risk patients, and 8.3% (1/12) high-risk patients (p = 0.632).

After excluding 41 patients with more rounds of ^{131}I administration or operation, which might additionally affect the change in Tg level caused by RAT, the median Tg_{on} value in the remaining 213 patients significantly decreased over time. Similar trends of change in median Tg_{on} level in patients with hyperthyroglobulinemia primarily caused by thyroid remnant, biochemical disease, and structural/functional disease were found (Fig. 6).

DISCUSSION

In this prospective multicenter study, we comprehensively reported the outcomes of RAT in a cohort of 254 TT-DTC patients with unexplained postoperative hyperthyroglobulinemia. Along with the non-S/FIR rate of 81.5%, a cause of biochemical/functional/structural disease and an intermediate-high risk were deemed in 82.7% and 94.1% of all eligible subjects, respectively, which was reached by a sufficient follow up post RAT with the initial administration of 5.55 GBq of ^{131}I. These novel findings may play a vital role in elucidating the indication for RAT, facilitating nuclear medicine practice and interdisciplinary communications.

Instead of the latest version, the original risk stratification protocol derived from 2009 ATA guidelines was timely adopted and feasibly applied in this study, avoiding commonly

insufficient detailed data on lymph node involvement and molecular features, which have been additionally suggested by 2015 ATA guidelines. In addition, the risks were merely assessed before and soon post RAT, evading potentially replacement by response categorization, so-called dynamic risk stratification in some previous studies (*13,14*). As a result, up to 93.3% TT-DTC patients with unexplained postoperative hyperthyroglobulinemia were initially classified as ATA intermediate-high risk during the interval between surgery and RAT. Unexpectedly, the distributions of risk before and after RAT were similar, indicating a stable and intermediate-high risk-predominant stratification in this commonly encountered entity. This may be interpreted by strictly controlled indications for total thyroidectomy, rigorous exclusion criteria of this study, and a pathological feature-predominant risk stratification scheme. Notably, although less than 1% of patients initially ranked as intermediate-risk were re-classified into high-risk immediately after RAT, as high as 11.8% of patients initially classified as low-risk were re-classified into intermediate-risk via post RAT scan. This modulation suggests that initially low-risk TT-DTC patients with hyperthyroglobulinemia may need more active monitoring and aggressive intervention instead of observation or RRA, which necessitates randomized controlled studies to evaluate the impact of RAT on prognosis (*15*).

During a median follow up of 10.6 months, hyperthyroglobulinemia was attributed to three well-defined causes. Using 5.55 GBq of ^{131}I, hyperthyroglobulinemia was finally attributed to thyroid remnant in only 17.3% of patients. Considering its high efficacy in

RRA recently demonstrated by our team (*11*), we believe that such dose is more competent for less thyroid remnant in the current study. Meanwhile, more than half of the patients with unexplained hyperthyroglobulinemia were causally categorized into biochemical disease, indicating the existence of sub-clinical lesions, which are most suitable for RAT and regular follow up under TSH suppression (*16*). Although a significant difference in median Tg_{off} level was found among the three cause groups, it is currently difficult to separate patients with structural/functional disease efficiently by Tg level from those with thyroid remnant or biochemical disease before RAT, much less do RAIU. In addition, distant metastases were identified by post RAT scan in less than 1% of patients with no apparently anatomic abnormalities, but favorable status after active treatment was noted. We tentatively conclude that the total tumor burden might be relatively light, and that RAT with 5.55 GBq of ^{131}I can identify and treat the lesions competently.

It has been acknowledged that patients with S/FIR require a more intensive follow-up than those with non-S/FIR (*1,17,18*). Conversely, a non-S/FIR means a < 1% rate of disease-specific death (*1,19*). The current study revealed no significant difference in response to RAT among the three risk groups, manifesting that RAT using a high activity of 5.55 GBq can yield similar short-term efficacies among the three-tiered risk groups.

In addition to acting as an efficient biomarker for postoperative disease status, Tg has long been recognized as a reliable therapeutic response evaluation tool (*15,20,21*). In our study, a significant decline in Tg level during as long as 1 year of follow-up in RAT-treated

patients was found regardless of the cause of hyperthyroglobulinemia, which may be explained by both the sustained destroying effect of ^{131}I on thyroid remnant and/or invisible ^{131}I-avid prmDTC lesions and the continuously sufficient suppression of TSH (*18,22*). Since it has been reported that patients had negative findings on post therapeutic ^{131}I scan, US, CT, and ^{18}F-FDG PET/CT but elevated Tg rarely showed positive findings on the 2nd ^{131}I scan (*23*), we recommended that patients without visualized ^{131}I-avid lesions be monitored under continued TSH suppression in the first-year post RAT. Moreover, since the Tg values just before RAT might be influenced by both TSH level and time interval between total thyroidectomy and RAT, thyroid hormone withdrawal for 4 weeks after total thyroidectomy when the median TSH level had climbed up to 100 mIU/mL (range, 49.5-100 mIU/mL) adequately assured both cleanup of existing serum Tg immediately after total thyroidectomy and exposure of Tg deriving from microscopic thyroid remnant and/or prmDTC lesion (*1*).

Although the term RAT has been raised for decades and attempts were recently made to define it as "^{131}I administered to destroy subclinical tumor deposits after surgical resection of all known primary tumor tissue and metastatic foci," a clear definition of "subclinical tumor deposits" was not achieved by the joint statement (*24*). Even more confusingly, the statement has also mentioned that patients with biochemical evidence of disease can also be candidates for RT like patients with structural/functional disease (*1,24*). The above difficulties and inconsistencies may be caused by the severe overlap of Tg level and

potentially simultaneous goals among the three clinical scenarios (RRA, RAT, and RT) and the absence of precisely differential techniques, necessitating diagnostic radioiodine scan and other imaging modalities (*25*). As was demonstrated by the current study, unexplained hyperthyroglobulinemia in TT-DTC patients represents an apparent indicator for RAT irrespective of the initial risk stratification, since over 90% patients in this entity were stratified as intermediate-high risk and 82.7% patients were finally attributed to biochemical/functional/structural disease. Therefore, we believe that our findings may ameliorate the relatively vague indication of RAT compared with those of RRA and RT, and constructively promote scientific dialogue.

The current study has some limitations. First, due to long-term controversies, diagnostic radioiodine imaging, which would have possibly explained the cause of hyperthyroglobulinemia in part before RAT, was not incorporated in our study. Second, since the optimal administered activity of ^{131}I in RAT had not been determined, our patients received a fixed activity of ^{131}I, thus, studies comparing outcomes and side effects of multiple doses are still needed. Third, a coming randomized control study assessing long-term outcomes may strengthen the significance of RAT by compensating this single-arm study.

CONCLUSION

Our prospective multicenter study demonstrated that unexplained hyperthyroglobulinemia in TT-DTC patients represents an appropriate indicator for RAT, since intermediate-high risk of carrying prmDTC was stratified in greater than 90% of patients and RAT with an activity of 5.55 GBq revealed biochemical/functional/structural disease and yielded non-S/FIR in more than 80% of subjects.

ACKNOWLEDGEMENTS

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DISCLOSURE

No conflicts of interest.

KEY POINTS

QUESTION: How should TT-DTC patients with unexplained hyperthyroglobulinemia be treated?

PERTINENT FINDINGS: Our prospective multicenter cohort study demonstrated that over 90% of TT-DTC patients with unexplained hyperthyroglobulinemia were stratified as intermediate-high risk, and RAT at a dose of 5.55 GBq revealed biochemical/functional/structural disease and yielded non-structural/functional incomplete response in more than 80% of subjects. Distribution for either cause of hyperthyroglobulinemia or response to RAT was comparable among the three postoperative risk groups.

IMPLICATIONS FOR PATIENT CARE: These findings recommend TT-DTC patients with unexplained hyperthyroglobulinemia as candidates for RAT irrespective of postoperative risk stratification.

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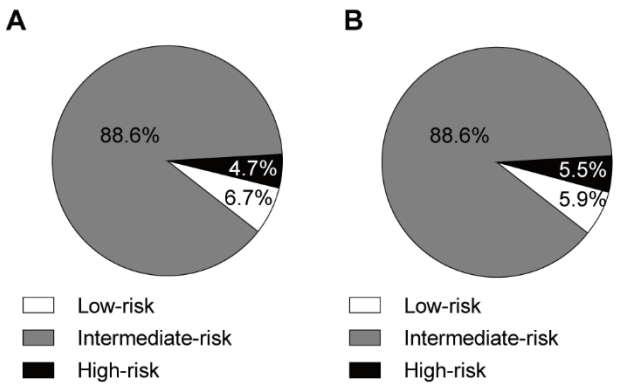

FIGURE 1. Risk stratifications in patients with unexplained hyerthyroglobulinemia before (A) and just after (B) radioiodine adjuvant therapy (N = 254).

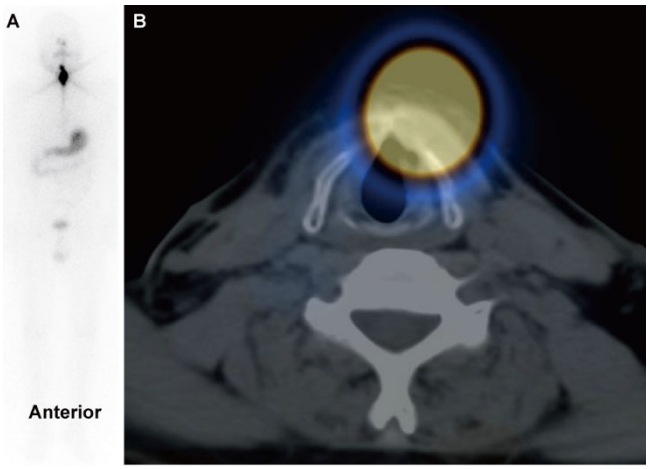

FIGURE 2. Post radioiodine adjuvant therapy whole-body scan (A) and SPECT/CT fusion image (B) of a papillary thyroid carcinoma patient with unexplained hyerthyroglobulinemia causally attributed to thyroid remnant.

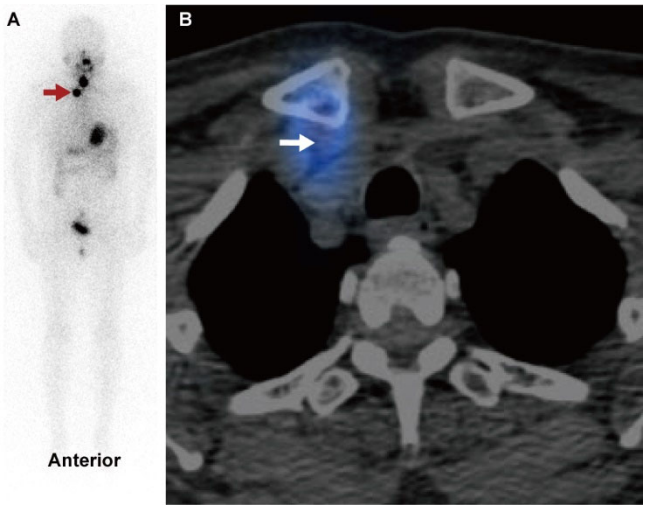

FIGURE 3. Post radioiodine adjuvant therapy (RAT) whole-body scan (A) and SPECT/CT fusion image (B) of a papillary thyroid carcinoma patient with unexplained hyerthyroglobulinemia causally attributed to a metastatic lymph-node (arrow) unable to be diagnosed by ultrasonography and CT before RAT.

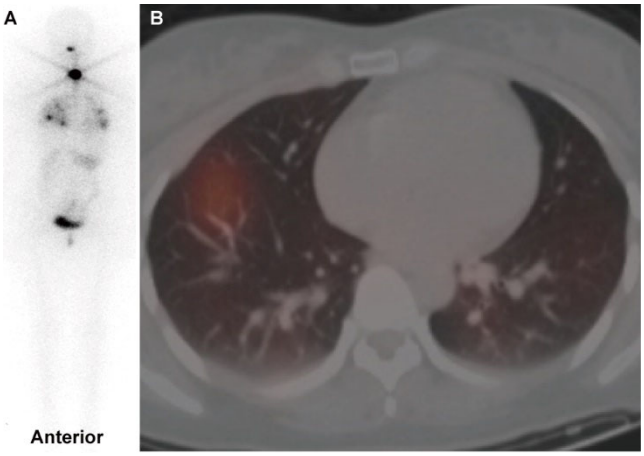

FIGURE 4. Post radioiodine adjuvant therapy (RAT) whole-body scan (A) and SPECT/CT fusion image (B) of a follicular thyroid carcinoma patient with unexplained hyerthyroglobulinemia causally attributed to lung metastases unable to be identified by CT before RAT.

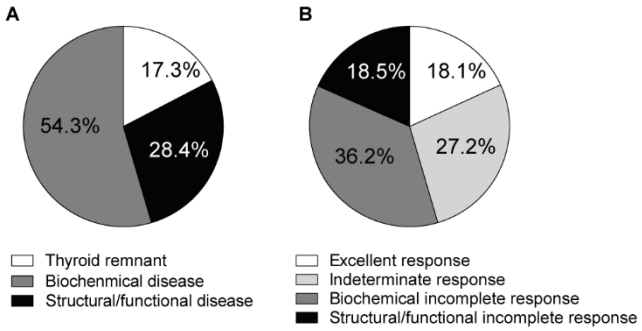

FIGURE 5. The causal distribution of unexplained postoperative hyerthyroglobulinemia post radioiodine adjuvant therapy (RAT) (A) and therapeutic response to RAT (B) (N = 254).

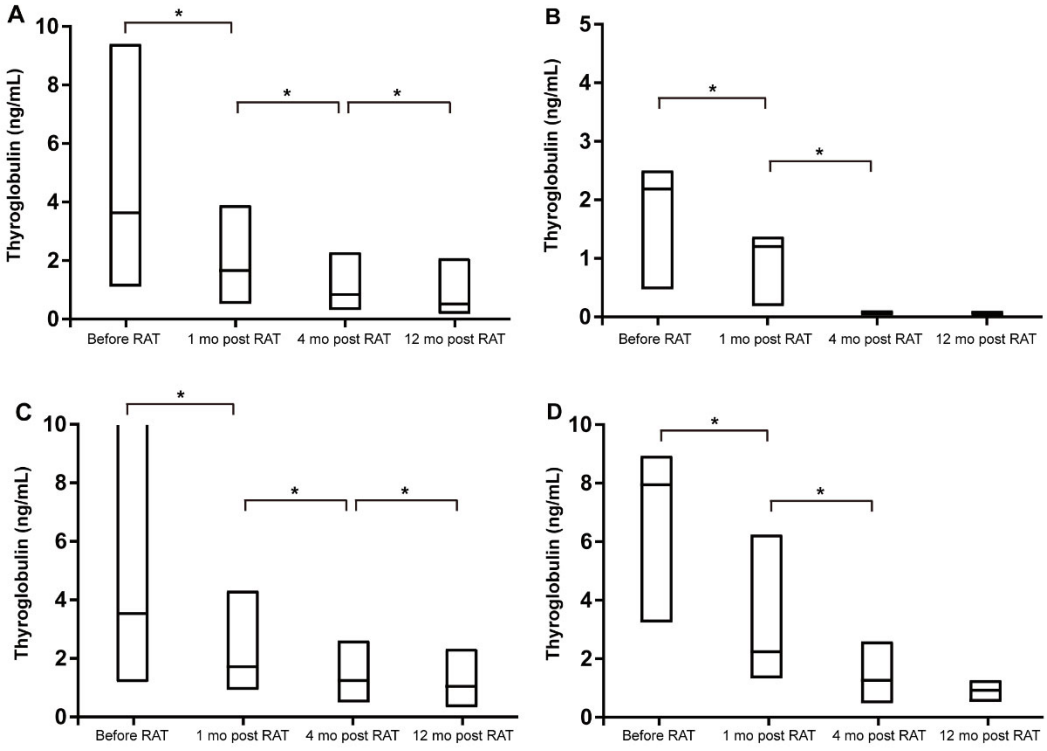

FIGURE 6. The change in suppressed thyroglobulin value in patients with unexplained hyperthyroglobulinemia who received only radioiodine adjuvant therapy. A: all patients (N = 213). B, C, and D: patients with unexplained hyperthyroglobulinemia casually attributed to thyroid remnant (N = 44), biochemical disease (N = 138), and structural/functional disease (N = 31), respectively. Data are expressed as median with interquartile range. *, $p < 0.05$.

Table 1. Baseline characteristics of totally thyroidectomized differentiated thyroid cancer patients with postoperative unexplained hyperthyroglobulinemia (N = 254).

Characteristics	Number (%)
Age	
<55 y	220 (86.6)
≥55 y	34 (13.4)
Gender	
Female	158 (62.2)
Male	96 (37.8)
Pathological subtype	
Papillary	248 (97.6)
Follicular	6 (2.4)
pT stage	
T1	154 (60.6)
T2	44 (17.3)
T3	29 (11.4)
T4	15 (5.9)
Tx	12 (4.7)
pN stage	
N0	13 (5.1)
N1	223 (87.8)
Nx	18 (7.1)
Stage	
I	230 (90.5)
II	22 (8.7)
III	2 (0.8)
Postoperative Tg_{on}-median (IQR) (ng/mL)	3.7 (1.3-9.3)
Postoperative Tg_{off}-median (IQR) (ng/mL)	27.1 (16.1-47.1)
TSH at 4 weeks after THW-median (range) (mIU/mL)	100 (49.5-100)
24h RAIU -mean ± SD (%)	4.7 ± 3.1
Visualization of thyroid bed on post RAT scan	249 (98.0)

TSH, thyroid-stimulating hormone; THW, thyroid hormone withdrawal; Tg_{on}, thyroglobulin level under TSH suppression with levothyroxine; Tg_{off}, thyroglobulin level under TSH stimulation; IQR, interquartile range; RAIU, radioactive iodine uptake; SD, standard deviation; RAT, radioiodine adjuvant therapy.

Table 2. Causal classification regarding postoperative risk of persistent/recurrent/metastatic differentiated thyroid cancer (DTC) in totally thyroidectomized DTC patients with unexplained hyperthyroglobulinemia (N = 254).

Risk-n (%)	Thyroid remnant-n (%)	Biochemical disease-n (%)	Structural/functional disease-n (%)	*p*
Low-17 (6.7)	5 (29.4)	8 (47.1)	4 (23.5)	
Intermediate-225 (88.6)	36 (16.0)	123 (54.7)	66 (29.3)	0.526
High-12 (4.7)	3 (25.0)	7 (58.3)	2 (16.7)	

Table 3. Comparisons of RAIU, TSH, Tg_{off}, and TgAb levels among three primary causes of unexplained hyperthyroglobulinemia in totally thyroidectomized differentiated thyroid cancer patients (N = 254).

Factor	Thyroid remnant	Biochemical disease	Structural/functional disease	*p*
RAIU (mean ± SD)	5.2 ± 3.2	4.6 ± 3.1	4.9 ± 3.3	0.964
TSH-median (range)	100 (49.5-100)	100 (49.6-100)	100 (56.6-100)	0.225
Tg_{off}-median (IQR)	17.0 (12.7-25.5)	26.9 (16.6-48.9)	33.5 (22.2-67.8)	0.000
TgAb-median (range)	10 (10-64.4)	10 (10-80.34)	10.5 (10-62.9)	0.227

RAIU, radioactive iodine uptake; TSH, thyroid-stimulating hormone; $Tg_{off,}$ thyroglobulin level under TSH stimulation; IQR, interquartile range. TgAb, anti-Tg antibody.