Undetectable pre-ablation thyroglobulin levels in patients with differentiated thyroid cancer: it is not always what it seems

Níveis indetectáveis de tireoglobulina pré-ablação em pacientes com câncer de tireoide: nem sempre é o que parece

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ABSTRACT

Objective: To establish the frequency of UTg (undetectable pre-ablation thyroglobulin) in TgAb-negative patients and to evaluate the outcome in the follow-up. **Subjects and methods:** We retrospectively reviewed 335 patients' records. Twenty eight patients (9%) had UTg. Mean follow-up was 42 ± 38 months. All subjects had undergone total thyroidectomy, and lymph nodes were positive in 13 (46%) patients. Tg and TgAb levels were measured 4 weeks after surgery by IMA technology in hypothyroid state. No evidence of disease (NED) status was defined as undetectable (< 1 ng/mL) stimulated Tg and negative Tg-Ab and/or negative WBS, together with normal imaging studies. **Results:** Seventeen patients (61%) were considered with NED. Four patients (14%) had persistent disease (mediastinum, n = 1, lung n = 2, unknown n = 1), and 7 (25%) had detectable TgAb by other method during their follow-up. **Conclusions:** UTg levels usually is associated to a complete surgery. However, in a low percentage of patients, this may be related to false negative Tg or TgAb measurement. Arq Bras Endocrinol Metab. 2013;57(4):300-6

Keywords
Undetectable thyroglobulin levels; thyroglobulin; ablation; thyroid; cancer

RESUMO

Objetivo: Estabelecer a frequência de U Tg (tireoglobulina indetectável pré-ablação) em pacientes com TgAb negativo e avaliar o prognóstico no seguimento. **Sujeitos e métodos:** Foram analisados retrospectivamente 335 registros de pacientes. Vinte e oito pacientes (9%) tiveram U Tg. O acompanhamento médio foi de 42 ± 38 meses. Todos os participantes receberam uma tireoidectomia total, e os linfonodos foram positivos em 13 (46%) pacientes. Tg e TgAb foram medidos quatro semanas após a cirurgia pelo método IMA em estado de hipotireoidismo. A não evidência de doença (NED) foi definida como níveis indetectáveis (<1 ng/mL) de Tg estimulada com anticorpos anti-Tg negativos e/ou PCI negativo, com estudos de imagem normais. **Resultados:** Dezessete pacientes (61%) foram considerados com NED. Quatro pacientes (14%) tiveram doença persistente (mediastino, n = 1, pulmão n = 2, n = desconhecido 1), e 7 (25%) apresentavam anticorpos anti-Tg detectáveis por outro método durante acompanhamento. **Conclusões:** U Tg geralmente indica uma cirurgia completa. No entanto, em uma pequena porcentagem de pacientes, pode estar relacionada com uma medida de Tg ou de anticorpos anti-Tg falsamente negativos. Arq Bras Endocrinol Metab. 2013;57(4):300-6

Descritores
Níveis de tiroglobulina indetectáveis; tireoglobulina; câncer; tiroide

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INTRODUCTION

Serum thyroglobulin (Tg) is usually used as a post-surgical marker to define disease status in patients with differentiated thyroid cancer (1,2). Up to 20% of patients may present Tg-Antibodies (TgAb), which might obscure the evidence of detectable Tg (3,4). TgAb are also considered as surrogate markers for the persistence of disease (1,2,6-8).

Variability in the detection of TgAb according to the methodology employed (immunometric, IMA *vs.* radioimmunometric, RIA) is a well-known situation with many specimens with interfering TgAb being misclassified as TgAb-negative when manufacturer-recommended cutoff values are considered (9). This situation is even more complex when patients are followed up with measurements by different methods, as it is common practice in Argentina, mainly when patients are evaluated in private practices.

On the other hand, undetectable pre-ablation stimulated Tg (U Tg) is a condition that might indicate complete previous surgery, secretion of non-immunoreactive Tg, or the presence of non-measurable serum TgAb (9-12).

The objective of this study was to establish the frequency of U Tg in patients with negative TgAb measured by IMA technology (considering the analytical sensitivity for each methodology), and to evaluate the outcome of these patients in the follow-up.

SUBJECTS AND METHODS

Approval from the review board of our institution was obtained for the study. We retrospectively reviewed the charts of 335 patients with diagnosis of differentiated thyroid carcinoma between January 2000 and May 2010: papillary thyroid cancer, n = 325 (97%), and follicular thyroid cancer, n = 10 (3%), who had undergone total thyroidectomy (with or without neck dissection), and were radioiodine-ablated after surgery in hypothyroid state (TSH levels > 30 mU/L). All included subjects had to have pre-ablation U-Tg associated with undetectable TgAb considering the analytical sensitivity as a cutoff value for each assay (IMA methodology), with no suspicion of metastatic systemic disease at diagnosis. Patients had to be followed up for at least 12 months after ablation.

Twenty eight patients met these criteria, 27 women and 1 man (Table 1). All of them were diagnosed with papillary thyroid cancer. The prevalence of U Tg in this series was 9%. Mean age of included patients was 48 ± 14 years, TNM Stages (*American Joint Committee of Cancer, 6th Edition*) were*:* Stage I: n = 17, Stage II: n = 2, Stage III: n = 5, Stage IV: n = 4. Risk of Recurrence according to the Latin American Thyroid Society (LATS) classification was: very low, n = 3; low n = 12; high n = 13 (2); and according to American Thyroid Association (ATA) was: low, n = 15, intermediate, n = 5, high, n = 8 (1).

Diffuse Hashimoto's thyroiditis was observed in the pathology of 11/28 (39%) of the patients. Mean follow-up for the full cohort of patients was 42 ± 38 months (range 13-153 months).

Methods

All included subjects received total thyroidectomy in a specialized center and lymph node dissection was performed in 18/28 (64%) patients.

Lymph nodes were dissected when intrasurgical anatomopathological analysis proved the presence of metastasis (frozen section). This was true for 8/18 (44%) patients (central and lateral neck dissection). In the remaining subjects, 10/18 (66%), lymph node dissection in the central neck compartment (level VI) was mostly indicated after confirmation of tumor size (T3) and/or when suspicious lymph nodes were noted during the surgical procedure. Five out of these 10 patients finally had metastatic microscopic central lymph nodes. In these series, the prevalence of lymph node metastasis was 46% (13/28 patients), as shown in table 1.

All patients received radioiodine thyroid remnant ablation. Mean radioiodine ablative activity was 123 ± 40 mCi 131-I. Tg levels were measured 4 weeks after surgery in the hypothyroid state (TSH > 70 mUI/L in all cases) and TgAb levels were assessed by IMA methodology in four different reference laboratories. Tg was measured by Elecsys Tg Electrochemiluminescence Immunoassay (Roche Diagnostics GmbH, Mannheim, Germany), which has a limit of detection of 0.5 ng/mL; Immulite 1000 and Immulite 2000 Tg Chemiluminiscence (Siemens Corp., Los Angeles, CA), with an analytical sensitivity (AS) of 0.2 ng/mL. For TgAb: Elecsys Anti-Tg Electrochemiluminescence Immunoassay (RSR Ltd., Pentwyn, Cardiff, U.K.). A value > 20 IU/mL was regarded as positive. Immulite chemiluminescent immunometric assay method was also used (Siemens Corp., Los Angeles, CA). Values > 20 kIU/liter were considered as positive.

Table 1. Characteristics of the 28 patients with papillary thyroid cancer with undetectable Tg levels after total thyroidectomy and radioiodine ablation

	n = 28 patients
Sex	
M/F	27 (96.5%)/1(3.5%)
Mean age (range)	48 ± 14 (27-73)
Papillary thyroid cancer	28 (100%)
Variant	
Classic	23 (82.5%)
Follicular	1 (3.5%)
Oncocytic	1 (3.5%)
Tall Cell	2 (7%)
Diffuse sclerosing	1 (3.5%)
TNM stage	
I	17 (61%)
II	2 (7%)
III	5 (18%)
IV	4 (14%)
ATA risk of recurrence	
Low	15 (54%)
Intermediate	5 (18%)
High	8 (28%)
Bilateral tumor	2 (7%)
Multifocal tumor	6 (21%)
LN metastasis	
Present	18 (64%)
Central	10 (71%)
Central and lateral	8 (29%)
No neck dissection	10 (36%)
Mean radioiodine dose for RA (mCi)	123 ± 40
Follow-up in months (range)	42 ± 38 (13-153)

Measurement of Tg and TgAb in different centers is a common practice in our country, as health care insurance companies reimburse the cost of laboratory tests according to their own agreement with specific institutions.

Follow-up

After thyroid remnant ablation, all patients were started on thyroid hormone therapy. Thyroid ultrasound scanning (US) was performed in all patients by using an 11 MHz linear array transducer every 6 months. Twelve to eighteen months after ablation, TSH-stimulated Tg was measured (in 18 patients after two 0.9 mg rhTSH administration and in 10 after thyroid hormone withdrawal). In 16/28 patients whole body scan (WBS) was also performed, in 6 after administration of 4 mCi of 131-I, and in the remaining 10 patients, after a new radioiodine dose (mean activity of 96 ± 40 mCi 131-I). No new radioiodine doses or diagnostic WBS were performed after 24 months of follow-up at the moment of the analysis.

In patients with measurable Tg in the follow-up (under L-T4 treatment or thyroid hormone withdrawal), and/or abnormal neck ultrasound, and/or persistence of TgAb after a 24-36 months of follow-up, morphological evaluations, including computed tomography (n = 5), and ^{18}fluorodesoxyglucose positron emission tomography (n = 3), were performed.

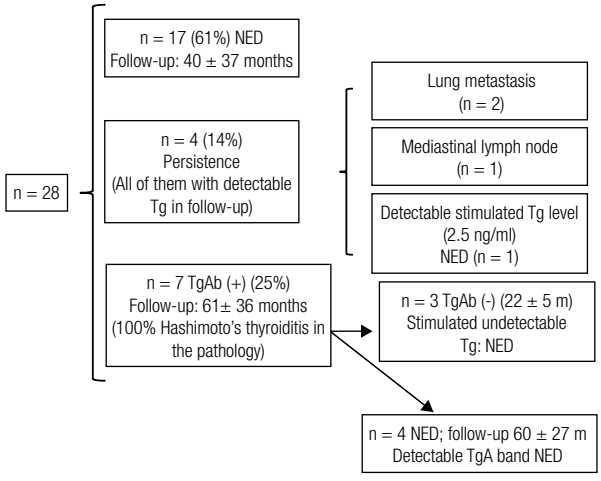
The *no evidence of disease* (NED) status was defined after the measurement of undetectable stimulated Tg in association with negative TgAb and/or negative diagnostic or post-dose WBS, together with ultrasonography and/or CT/MRI/PET-CT showing no evidence of disease.

Statistical analysis

Quantitative data were expressed as means and SD, and qualitative data were expressed in percentages.

RESULTS

The clinical characteristics of the 28 patients with U Tg are shown in table 1, and the outcome of these patients is presented in figure 1.



NED: no evidence of clinical disease; Tg: thyroglobulin; TgAb: anti-thyroglobulin antibodies; (+): positive; (-): negative.

Figure 1. Outcome of the 28 patients with thyroid cancer and undetectable pre-ablation thyroglobulin levels and negative TgAb.

Post-ablation WBS results showed only thyroid bed uptake in the neck in all 28 included subjects, except for one who had mediastinal uptake.

Seventeen patients (61%) were considered with NED. These patients were followed up for 40 ± 37 months after thyroid remnant ablation, and did not show any evidence of recurrent disease. In this group of patients, TNM stages were Stage I: n = 14 (82%); Stage II: n = 2 (12%) and Stage III: n = 1 (6%), and risk of recurrence (LATS) was: very low and low for n = 13 (76%) and high for n = 4 (24%), whereas ATA recurrence risk was: low n = 13 (76%) and intermediate n = 4 (24%).

Four patients (14%) had persistent/recurrent disease (mediastinum, n = 1, lung n = 2, unknown n = 1). The only patient with mediastinal persistence was diagnosed after abnormal uptake in the WBS after the first radioiodine activity of 100 mCi 131-I. Another radioiodine dose of 150 mCi 131-I was administered 12 months later, showing persistent mediastinal uptake, together with abnormal uptake in the same site with the ^{18}FDG in the PET/CT, and stimulated detectable Tg of 5.4 ng/mL. Mediastinal lymph node dissection was then indicated. One of 7 lymph nodes was positive for metastatic papillary thyroid carcinoma. A new stimulated Tg level, performed 12 months after surgery, showed persistent detectable Tg level of 2.4 ng/mL.

Both patients diagnosed with lung metastasis had a post ablation WBS showing only thyroid bed uptake (100 mCi 131-I). The appearance of detectable Tg level under thyroid hormone suppressive therapy (2.5 and 1.9 ng/mL, 12 and 24 months after remnant ablation, respectively) without any other suspicious finding (normal US and chest CT), led us to administrate a second radioiodine dose of 100 mCi 131-I. Post-dose WBS showed diffuse radioiodine uptake in the lungs associated with stimulated Tg level of 69 and 144 ng/mL, respectively. The fourth patient had biochemical persistence with a stimulated Tg level of 2.5 ng/mL measured 72 hours after two recombinant human TSH injections, without any other sign of disease localization. The TNM stages for three of these patients were IVa (two classic and one tall cell PTC variant), and one patient was staged as IVb with diffuse sclerosing variant of PTC. The risk of recurrence was high for all of them, according to both LATS and ATA classifications.

Seven patients (25%) presented TgAb detection by other IMA methodology in their follow-up (Table 2). All of these patients had diffuse Hashimoto's thyroiditis in the pathological analysis.

Table 2. Laboratory IMA used in the first negative TgAb assessment and in the second detectable TgAb measurement in 7 patients with papillary thyroid cancer

Patient	Baseline (undetectable)	Follow-up (detectable)
1	ChL (Immulite 1000 SM)	EChL (Elecsys 2010 R)
2	ChL (Immulite 2000 SM)	EChL (Elecsys 2010 R)
3	EChL (Elecsys 2010 R)	ChL (Immulite 1000 SM)
4	EChL (Elecsys 2010 R)	ChL (Immulite 2000 SM)
5	ChL (Immulite 1000 SM)	EChL (Elecsys 2010 R)
6	ChL (Immulite 1000 SM)	EChL (Elecsys 2010 R)
7	EChL (Elecsys 2010 R)	ChL (Immulite 2000 SM)

ChL: chemiluminescence; EChL: electrochemiluminescence.

Three of these 7 patients were finally considered with NED (undetectable Tg and TgAb in the follow-up). This situation ocurred 22 ± 5 months after remnant ablation. All were TNM stage I, but with high (LATS) or intermediate (ATA) risk of recurrence.

The remaining 4 patients still persisted with detectable TgAb, with no evidence of disease after a mean follow-up of 60 ± 27 months.

DISCUSSION

Thyroglobulin is a specific tumor marker when total thyroidectomy is performed and remnant ablation indicated. Most differentiated thyroid cancer cells synthesize Tg, although there may be differences in the molecular conformation of this tumor-derived Tg (13,14). The presence of detectable Tg after total thyroidectomy and remnant ablation usually indicates persistence or recurrence of disease (1). Pre-ablation stimulated Tg levels < 10 ng/mL under hypothyroid conditions has been proven to have a high negative predictive value in the definition of free of disease patients (15,16).

However, serum Tg measurement remains technically challenging even after 30 years of experience with different assays (17). Despite the introduction of a Tg reference preparation (CRM 457) more than 10 years ago (18), current methods to measure Tg still have an unacceptable intermethod variability (14,19), and this issue would need to be addressed before considering Tg as a marker of the presence of thyroid tissue. On top of that, false negative Tg levels from 4 up to 35% of DTC patients with evidence of local or metastatic disease have been reported in literature (20-24).

Interference of serum antibodies remain the most serious problem, limiting the clinical utility of Tg testing. Tg-Ab is usually detected in around 20% of patients

with DTC, compared with the 10% generally seen in the general population (20). The presence of TgAb is characterized by discordance in Tg values between RIA and IMA methodologies (detectable Tg using RIA and low or undetectable Tg using IMA) (14).

When TgAb are initially detectable, their serum level may decrease over subsequent months and years after adequate therapy, as thyroid tissue mass and Tg antigen levels decline (25,26). Patients may not achieve negative TgAb status during the first postoperative year, and may even exhibit a rise (or *de novo* appearance of TgAb during the 6 months after a radioiodine treatment, when there is release of Tg antigen secondary to lytic cell damage of thyroid tissue) (27,28). Clearly, it is the long-term trend in TgAb concentrations that is more valuable than any single TgAb level *per se* (29). Kim and cols. found that less than 1% of patients who became TgAb-negative or displayed more than 50% decrease in TgAb levels over the 6 to 12 months period after radioiodine treatment had recurrence detected during follow-up. In contrast, 19% of patients in whom TgAb decreased less than 50%, as well as the 37% in whom TgAb concentrations rose, were diagnosed with recurrence (29).

On the other hand, undetectable Tg levels at the time of ablation may reflect variable situations, according to different publications (12,16,30,31). Almost 30% of the reported patients in these series have an undetectable Tg levels after surgery. In our experience, finding undetectable pre-ablation stimulated Tg levels is not frequent, as it was shown in this study. In a retrospective investigation performed by the Thyroid Department (of the Argentinian Society of Endocrinology and Metabolism), more than 90% of patients had detectable Tg levels at the moment of ablation (16). Similarly, we had 9% of patients of our database with an undetectable pre ablation Tg level, and only 61% of them were considered free of disease. Whether this is a condition associated with the surgery technique usually employed in our country or to other circumstances, it remains unclear.

On the other hand, 14% of these patients with U Tg had persistent disease. In a study performed by Rosario and cols., the presence of undetectable Tg at the time of ablation enabled early prediction of long-term outcome of low risk patients (12). On the other hand, 57.7% of Park and cols. patients with U Tg but positive post-ablation WBS were stage III or IV, and they found regional and distant metastases in 42.3% of low risk patients (11). In the study of Phan and cols., who specifically analyzed low risk patients with undetectable Tg at ablation, only 3.4% of these patients had metastasis on postoperative US or WBS, suggesting that the measurement of a stimulated Tg at 12-18 months in order to define the disease status was unnecessary (10). We agree that this is true for most patients with U Tg, but we observed 14% recurrence (including distant metastatic disease not detected by the measurement of the first stimulated Tg). We believe that, in these cases, the method that had been used to measure the first stimulated Tg level did not detect it accurately, yielding a false negative value. Otherwise, Tg would not have been detectable on thyroid hormone suppressive therapy 12 and 24 months after thyroid remnant ablation.

Furthermore, 25% of our patients who had undetectable TgAb turned out to be positive in successive measurements with other laboratory kits (Table 2). It is probable that if we continued measuring TgAb with the same IMA methodology, we could have missed these positive TgAb cases.

Given the high prevalence of TgAb, it is critical to ensure that specimens do not contain TgAb before authenticating a serum Tg result, because even low levels of TgAb can interfere with Tg measurement (1,2,9,17). Interference of serum antibodies remain the most serious problem, limiting the clinical utility of Tg testing. Tg-Ab is usually detected in around 20% of patients with DTC, compared with the 10% generally seen in the general population (20). The presence of TgAb is characterized by discordance in Tg values between RIA and IMA methodologies (detectable Tg using RIA and low or undetectable Tg using IMA) (9,14).

Table 2 shows the different kits used for TgAb measurement in our series. Because of TgAb method variability, the same method needs to be employed for long-term monitoring. This requirement is problematic for laboratories because manufacturers sometimes withdraw or change their methods without any notification. Furthermore, it is not unusual for patients to change physicians and/or insurance plans that offer different laboratories to continue their follow-up.

Although undetectable pre-ablation Tg levels usually indicate complete previous surgery, our data reinforce earlier observations that, in a low percentage of patients, this situation may be related to non-detectable Tg or to the presence of TgAb (12-30,31). We believe that, when concurrent chronic thyroiditis is found by the pathologist, or when initial TNM stages are dis-

cordant with pre-ablation Tg levels, it is imperative to measure TgAb with different laboratory kits in order to avoid misdiagnosing a patient with undetectable Tg level as free of disease.

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