Anti-thyroglobulin antibodies in differentiated thyroid carcinoma patients: Study of the clinical and biological parameters

Anticorps anti-thyroglobuline chez les patients atteints de carcinome différencié de la thyroïde : étude des paramètres cliniques et biologiques

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Abstract

Objectives. – Detection of thyroglobulin in serum is of major clinical importance. The current assay techniques do not have all the qualifications which make the results of thyroglobulin difficult to interpret. The major problem is the autoantibody thyroglobulin (TgAb) interference. They induce an underestimation of thyroglobulin concentrations in the immunometric methods. We report in this study the clinical and biological parameters of anti-thyroglobulin antibodies of patients with differentiated thyroid carcinoma. Patients and methods. – A total of 246 patients with thyroid carcinomas were delicately selected from 2005 to 2012 in the nuclear medicine service of Tlemcen University hospital. Plasma thyroid stimulating hormone, thyroglobulin and anti-thyroglobulin antibodies were measured on Elecsys with the standardised Immunoradiometric assay. Results. – We noticed that there is a rapid increase in the annual number of cases of thyroid carcinoma detected since 2007 with a much higher incidence in women. The rate of anti-thyroglobulin antibody interference reached 20.40%. The distribution of positive anti-thyroglobulin antibodies is not related to age or sex. Conclusion. – It is recommended to systematically measure anti-thyroglobulin antibodies, in parallel with the determination of thyroglobulin, using a sensitive method.

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Résumé


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1. Introduction

Thyroglobulin is the protein precursor for the synthesis of thyroid hormones. It is detectable in the serum and its dosage is a real challenge [1]. The most immunometric current techniques do not have all the required qualities, which makes difficult the thyroglobulin results interpretation.
The international standard exists: CRM 457. A small number of companies do not however use it due to the great heterogeneity of the thyroglobulin molecule which affect its immunoreactivity.

The detection limit, interseries reproducibility and the possibility of a hook effect are the other features to be tested. The major problem is the interference due to the TgAb. They induce an underestimation of thyroglobulin concentrations in these immunometric methods [2].

No current assay is completely free of this interference. It is recommended to systematically measure thyroglobulin antibodies, in parallel with the determination of thyroglobulin, using a sensitive method. The recovery tests should be eliminated [3].

The interpretation of thyroglobulin assay results should reflect the thyroid status of the subject, the mass of thyroid tissue and stimulation of the receptor for thyroid stimulating hormone (TSH).

We were interested in this study to evaluate the interference of anti-thyroglobulin antibodies (ATA) in thyroglobulin (Tg) in the case of patients with thyroid cancer in Tlemcen university hospital.

2. Subjects and methods

This work was performed in the laboratory of nuclear medicine service in Tlemcen University Hospital (North-West Algeria). This is a retrospective study with subjects suffering from thyroid cancer who underwent a thyroidectomy and hospitalization in iratherapy service.

The period of patient recruitment was from 2005 until 2012.

2.1. Selection criteria

The study was focused on 316 patients. Patients were recruited through a software called NUCLEUS designed specifically to meet the many and varied needs of the service in the monitoring of thyroid disease.

The additional study of archived records has enabled us to complete some not mentioned in the computerized system and consequently retain only given to responding patients following selection criteria:

- patients that have undergone partial or total thyroidectomy;
- first hospitalization after the operation in the service of Nuclear Medicine;
- patients who have undergone a rhTSH stimulation aimed to increase the iodine fixation;
- first visit after undergoing treatment;
- patients scheduled for treatment with iodine-131 in the form of capsules.

Exclusion criteria were:

- patient undergoes thyroidectomy, but did not respond to the consultation;
- patient absent from his appointment of followed;

- patients whose appointment to a iratherapy not gone yet reached;
- patients whose removal was not in compliance with dosage (clotted blood, plasma hyper-lipidimic and haemolysed);
- lack of a result of the assays (TSH -Tg -ATA);
- results assay not consistent with quality control and ongoing results.

Only 246 patients reply to the selection criteria.

2.2. Methods

Patients were recruited on the day of their appointment in the service. The blood samples were collected in EDTA tubes. These tubes were centrifuged and aliquotted into microtubes labeled with patient name, case number, serial number and date of collection. These microtubes were classified according to the acts charged and then frozen at 18 °C.

The samples were thawed before assay.

Plasma TSH was measured with technical Immunoradiometricassay (IRMA) (125I, RIA-gnost® rhTSH, CISBio International).

Plasma thyroglobulin was measured on Elecsys (Elecsys® TG, Roche Diagnostics, France), the kit has a limit of quantitation of 0.7 ng/mL.

Anti-thyroglobulin antibodies (ATA) assay was performed according to the IRMA technique (125I-kit ABHTGK-3, Dia-Sorin, Antony, France), specifically for Human (ATA), with analytical sensitivity of 5 IU/mL.

The usual values in a population of healthy subjects are less than 100 IU/mL.

3. Results

The incidence of thyroid carcinoma was inspected during the seven past years in the service of Nuclear Medicine and is shown in Fig. 1. We noted a rapid increase in the annual number of cases of thyroid carcinoma detected since 2007, the number has increased by a factor of 2.74.

The distribution results of the number of patients studied by sex (Fig. 2) showed a clear dominance of thyroid cancer in women than men with a percentage of 86% for women against 14% for men.
The distribution of carcinomas by age classes showed (Fig. 3) that the prevalence is highest among adults whose age is between 26 and 65 years, with a maximum of around 24% in the age group between 36–45 years. However, a significant frequency (13%) occurred among adults under 26 years.

The analysis of the assay of rates of positive ATA showed (Fig. 4) that 76% of patients are negative for ATA while 24% of ATA is positive. The positive ATA is divided almost equally between women and men, and no link between gender and the impact of ATA could be highlighted. No difference in distribution of positive results according to the age groups ATA was shown between different ages and therefore there’s no link between the age of the patient and the positive impact of ATA.

The interference in the determination of Tg rate showed (Fig. 5) that 10 patients out of 39 have a negative thyroglobulin in the presence of ATA. It represents a rate of 20.40% of the interference of ATA in thyroglobulin.

4. Discussion

We are interested in this study to evaluate the interference of ATA and their impact in the disruption of the validation of assay results of the Tg. Interpretation of the results allowed us to develop the state current thyroid cancer in the western region of Algeria since the Nuclear Medicine service of Tlemcen and provides results of diseases of the thyroid gland of patients from the entire western and southwestern region.

We found a rapid increase in the annual number of cases clearly related to improving the completeness and recruitment since 2005. The number of new cases each year was between 15 and 30 cases [4,5]. The annual incidences observed in the world sometimes differ markedly, suggesting the involvement of multiple risk factors still poorly understood, food, ethnic or environmental [6]. Thus, thyroid cancers are more common in women than men regardless of the morphological type studied with a rate of 86% of the study population. Some reports studied this phenomenon and explain it by predisposition favoured by the emotional fragility of the woman through its hormonal activity constantly changing and certain genetics [7]. The distribution by age showed us that the prevalence is highest among adults whose age is between 30 and 60 years, but with a frequency not excluded in less than thirty years. This contrasts with the data presented by Vander et al. (1968) [8].

Thyroid cancer is a rare disease, accounting for less than 1% of the causes of cancer death, but it has the distinction of reaching young subjects including child [9].

Plasma thyroglobulin is widely used as a tumor marker for the detection of recurrences and monitoring of differentiated thyroid cancers. This essay usually shows a good correlation between the levels of Tg and the mass of differentiated thyroid tissue. But it should be noted that there are analytical problems encountered, the most are standardization, technical sensitivity, reproducibility interseries, the presence of the hook effect, and of course the interference by TgAb.
The high rate of ATA after chirurgical act or metabolic radiotherapy is not exceptional because the physical damage of the thyroid tissue and represents a significant rate in the population covered by our study, which is 24%. However, it was demonstrated that decrease or undetectable levels of ATA after surgery seem to be a good prognosis. In contrast, the ATA rates remaining stable or elevated in patients with the evolving times sign the persistence of antigenic stimulation in relation to the presence of ectopic thyroid residues [10].

Our study showed that sex and age do not have a significant impact in the presence of remnant after suppression therapy following thyroidectomy. The frequent presence of ATA (in 24% of patients) poses problems of interpretation of thyroglobulin. To reduce this interference, manufacturers have used monoclonal or polyclonal antibodies with higher affinity TgAb [2,3]. The interference of ATA is the most serious problem in the assay of Tg. Interference of ATA in the immunoradiometric assay of Tg in the ATA positive patients in our study represents a ratio of 1 in 5 cases and suggest that ATA should be measured in all patients treated for thyroid differentiated cancer in order to validate the determination of Tg [11].

It was noted a variable correlation for anti-Tg antibody levels when the same samples were measured using 6 different assays (3 immunometric and 3 radioimmunoassays [12]). This result was also reported by Spencer et al. [13], who reported that among 143 patients in whom positive anti-Tg antibodies were detected, only 35–62.2% were detected on 1 or more of 3 IMAs. In clinical practice, this variability presents a challenge when determining whether an individual patient has an accurate Tg measurement and also whether anti-Tg antibody levels are used as a biochemical marker of tumor progression or persistence. It is important to recognize that the lower limit of detection of anti-Tg antibodies is a possible partial cause of the discordance.

Indeed, when the “cutoff” was lowered to the lowest limit of accurate assay detection, rather than the reference range for an individual assay, greater concordance was observed [14]. Thus, for patients with thyroid cancer, it is our approach to use the lower limit of detection, rather than the lower part of the normal range to define the presence of anti-Tg antibodies. This should also be determined by individual laboratories. Another potential cause of discordance is the heterogeneity of Tg epitopes to which the antibodies are directed and their recognition in the different anti-Tg antibody assays [12,14]. For these reasons, when managing patients with proven or suspected DTC who have undetectable Tg and anti-Tg antibody results, it is reasonable to repeat the measurements using a different method to enhance confidence that undetected anti-Tg antibodies are not the cause of the discordance.

5. Conclusion

The interpretation of plasma Tg used in the monitoring of differentiated thyroid cancers should be very cautious because of the many factors surrounding the determination of Tg. This is mainly to ensure the patient pituitary (TSH), and detection of ATA (assay ATA) that can disturb the determination of Tg by technical IRMA. The discovery of aberrant biological results requires collaboration between the clinician and biologist for optimal management of thyroid diseases.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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