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Calcitonin Screening in Nodular Thyroid Disease: Is There a Definitive Answer?

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Abstract
Introduction: Calcitonin (Ctn) is a hormone secreted by thyroid "C" cells and is considered an excellent marker for medullary thyroid carcinoma (MTC). However, the use of Ctn to screen patients with nodular thyroid disease (NTD) remains controversial. ***Objective:*** The aim of this work was to define the frequency of hypercalcitoninemia among NTD patients followed at a tertiary referral hospital. ***Methods:*** A retrospective analysis was made of basal Ctn measurements and corresponding patients' records between January 2011 and December 2015. Hypercalcitoninemia was defined as >10 pg/mL. Depending on the Ctn value, three groups were considered: G1, ≤10 pg/mL; G2, 10–100 pg/mL; G3, ≥100 pg/mL. ***Results:*** Ctn was requested in an NTD context for 1,504 patients, 69 of whom had hypercalcitoninemia. Of these, 20 underwent surgery (G2, 11; G3, 9), and a histological diagnosis of MTC was established in 12 (G2, 3/27%; G3, 9/100%). Surgery was chosen based solely on Ctn levels in 7 cases, since only 5 had a positive cytology. ***Conclusions:*** Hypercalcitoninemia was found in 4.6% of NTD patients. Ctn levels ≥100 pg/mL were associated with a greater CMT risk than values between 10 and 100 pg/mL, reinforcing results from other groups. The need for an adequate interpretation of results as well as an appropriate selection of patients to surgery stresses the importance of endocrinologists requesting and interpreting results.

Introduction

Calcitonin (Ctn) is a 32-amino acid polypeptide secreted by the parafollicular cells of the thyroid, called "C" cells. With a known important role in regulating blood calcium in fish and rodents, the role of Ctn in human calcium homeostasis remains uncertain [1].

Medullary thyroid carcinoma (MTC) originates from "C" cells. It is well established that Ctn is a valuable tumor marker in patients with MTC and its serum concentration is directly related to "C" cell mass [2, 3]. Besides tumor markers, Ctn measurement is considered the most sensitive tool for detecting "C" cell disease – a preneoplastic condition. However, MTC is rare, corresponding to only 3–10% of all thyroid cancers; MTC in patients with nodular thyroid disease (NTD) has been reported to range from 0.3 to 1.4% [2, 4, 5].

There is evidence that serum Ctn measurement in patients with thyroid nodules can result in earlier detection of MTC and/or "C" cell hyperplasia, prior to malignant transformation, in individuals with a familial history of

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Table 1. Patients submitted to surgery: individual data

Patient No.	Gender	Age, years	Ctn value, pg/mL	Cytologic result	Histologic result	Other relevant histologic features
1	M	66	17.6	–	Follicular hyperplasia	–
2	F	45	16	Benign	PTC	–
3	F	32	11.1	PTC	PTC	–
4	M	58	22.6	Follicular tumor	FTC (oncocytic)	–
5	M	67	13.5	Benign	FTC	–
6	M	65	23.5	Benign	PTC	–
7	M	67	20	–	PTC	–
8	M	80	65.1	Benign	Follicular adenoma	–
9	M	61	15.4	Benign	MTC	–
10	M	73	11.3	–	MTC (micro)	PTC (micro)
11	F	64	15.9	Benign[1]	MTC (micro)	PTC (micro)
12	F	73	209	Benign	MTC	–
13	M	69	365	MTC	MTC	–
14	M	75	248	Papillar	MTC (micro)	–
15	M	24	1,674	MTC	MTC	–
16	F	42	588	MTC	MTC	–
17	F	66	1,212	MTC	MTC	–
18	F	40	1,978	Undetermined	MTC	–
19	F	52	645	MTC	MTC	–
20	M	68	3,387	Benign	MTC	–

MTC, medullary thyroid carcinoma; PTC, papillary thyroid carcinoma; –, no data.
[1] Cytology-histology noncorrelation.

MTC. This is of great importance considering that surgery is the first-line treatment and its efficacy depends on the local extent of the disease. On the other hand, the rare prevalence of MTC in patients with nodular disease raises concerns regarding cost-effectiveness in routine serum Ctn measurements in this population [2, 4–7].

Moreover, we have to be aware that other pathological conditions may respond for elevated Ctn levels. In fact, only 10–40% of patients with elevated basal Ctn levels associated with a thyroid nodule are ultimately diagnosed with MTC [8]. Additionally, falsely elevated levels of Ctn may result from the assay used or from the presence of heterophilic antibodies [2, 8].

Today there is still no consensus about Ctn screening in patients with thyroid nodules for MTC diagnosis. This practice is the standard of care at reference centers in Europe; however, the American Thyroid Association does not recommend for or against this practice.

This study intended to define the frequency of hypercalcitoninemia among NTD patients followed at a tertiary referral hospital. As a secondary endpoint, we aimed to define the prevalence of MTC among NTD patients with raised levels of Ctn.

Methods

Retrospective analysis of basal serum Ctn measurements was performed at our center between January 2011 and December 2015, and revision of the corresponding clinical records was undertaken. As the study was a retrospective and anonymous analysis of data there was no need for consent.

Ctn measurements were performed using an immunochemiluminescent assay (IMMULITE® 2000), with an upper 95% range of 8.4 pg/mL for males and 5 pg/mL for females.

The exclusion criteria were absence of clinical information, and no evidence of NTD or individuals with a familial history of MTC. Hypercalcitoninemia was defined as a basal Ctn value >10 pg/mL based on an in-house study of the normal range. Using the concept introduced by Costante et al. [6] in order to facilitate data interpretation, patients were grouped into three different sets according to Ctn value: group 1 (G1), Ctn value <10 pg/mL; group 2 (G2), Ctn value between 10 and 100 pg/mL; group 3 (G3), Ctn value >100 pg/mL. The diagnosis of MTC was established based on a pathological report.

Results

A total of 1,504 cases were identified with clinical information available and evidence of NTD. Hypercalcitoninemia was documented in 69 cases (G2, $n = 57$, and G3,

$n = 12$); in other words, 4.6% of NTD patients had values above 10 pg/mL. Twenty patients were submitted to surgery (G2, $n = 11$, and G3, $n = 9$), with a total of 12 MTC cases diagnosed (G2, $n = 3$, and G3, $n = 9$). Of these, only 5 (42%) had a positive cytology. The individual data are depicted in Table 1. Adverse events were not reported.

Three out of the 12 MTC cases were microcarcinomas from which 2 coexisted with a micropapillary thyroid carcinoma. All of the patients denied a family history. Genetic testing for *RET* germline mutations was conducted in 7 cases and was positive in 1 case from G3.

Forty-nine patients with hypercalcitoninemia (46 classified as G2 and 3 as G3) were not submitted to surgery. A few are currently waiting surgery and the majority are under surveillance.

Discussion

MTC is a neuroendocrine tumor derived from the parafollicular cells that secrete Ctn; it can be either sporadic or inherited. *RET* germline mutations have been ascertained as the underlying mechanism of familial cases. *RET* somatic mutations are also found in about 45% of sporadic MTCs, indicating a poor prognosis [9–11].

Serum Ctn levels represent a high value tumor marker either preoperatively or during follow-up [12]. Surgery is the gold standard treatment and the possibility of a cure depends on an early diagnosis.

In the current series of 1,504 patients, hypercalcitoninemia, defined as a value above 10 pg/mL, was documented in 69 cases (4.6%), representing a frequency similar to that reported for a Brazilian population [8]. Results would be different for a higher cut-off, eventually reducing the false positive cases. However, the gray area between normal and abnormal values is still a limitation to defining an unquestionable cut-off.

Of those submitted to surgery (29%), 60% proved to have MTC and 90% had a thyroid carcinoma. In all cases, the false positive for MTC corresponded to values of Ctn <100 pg/mL (range 11.1–65.1 pg/mL). Among these, the histological diagnoses were: follicular hyperplasia ($n = 1$), follicular adenoma ($n = 1$), papillary thyroid carcinoma ($n = 4$, 2 microcarcinomas), and follicular carcinoma ($n = 2$). The high prevalence of malignancy in this subgroup suggests a surgical decision based not only on Ctn values, but also on other clinical criteria. On the other hand, the hypothesis of a secondary hypercalcitoninemia resulting from substances released by these tumors with a paracrine stimulatory action on "C" cells cannot be ruled out.

The prevalence of MTC among patients with NTD has been reported as ranging from 0.3 to 1.4%. The retrospective nature of our study, and the fact that not all patients with hypercalcitoninemia were operated, makes us unable to calculate the MTC frequency in the current series.

The routine measurement of serum Ctn in patients with thyroid nodules is a matter of debate. While for the majority of European authors serum Ctn measurement should be performed in the presence of NTD, the American Thyroid Association guidelines do not recommend either for or against this.

The low frequency of MTC and the possibility of false positive results raise two main concerns: (1) cost-effectiveness and (2) surgical risks for hypoparathyroidism and vocal cord palsy. Cheung et al. [5] assert that routine serum Ctn screening in patients undergoing evaluation for NTD appears to be cost-effective in the USA, with cost-effectiveness comparable to the measurement of thyroid-stimulating hormone, colonoscopy, and mammography screening.

In our series, the sensitivity of serum Ctn was higher than that of cytology by fine-needle aspiration, as reported by others [6, 13–16]. As a matter of fact, on fine-needle aspiration cytology only 45.5% of cases were categorized as MTC. In a meta-analysis, the accuracy of cytology in diagnosing MTC was under 50% [17]. Even admitting that a number of micro-MTC cases might not progress, the aggressiveness of the majority of MTC cases points in favor of a surgical approach.

There are several conditions, both physiological and pathological, that may raise serum Ctn. The most common are: use of proton pump inhibitors, β-blockers, and glucocorticoids; Hashimoto thyroiditis; renal insufficiency; follicular and papillary thyroid carcinomas; C-cell hyperplasia, and neuroendocrine tumors [8, 18, 19].

Measurement of serum Ctn and the finding of a borderline value does not imply immediate surgery. The previously suggested cut-off of 100 pg/mL [6, 8, 18] is reinforced by our results. However, even if MTC is present, for values below 100 pg/mL, there is time for other examinations, such as immunocytochemistry, measurement of Ctn in the needle washout fluid after cytology [1, 6, 20, 21], and/or stimulation tests using Ctn secretagogues (pentagastrin or calcium infusion). However, pentagastrin is not always available despite being the most used secretagogue. In patients with neuroendocrine tumors other than MTC, serum Ctn levels do not increase in response to pentagastrin or calcium stimulation, contributing for the differential diagnosis [18, 19, 22].

In conclusion, measurement of serum Ctn is a diagnostic tool of unconditional importance for MTC, with a greater

sensitivity than cytology. Clinicians have to be aware of false positives but must also consider that missing an MTC diagnosis may have a negative impact on the outcome of affected individuals. The difference between a curative thyroidectomy and the need for more than one surgery and persistence of disease should be considered. A judicious interpretation of results is of utmost importance and is more likely to be achieved when performed by an expert endocrinologist.

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Statement of Ethics

The study was approved by the Ethical Commission of the Medical Academic Center of Lisbon (CAML).

Disclosure Statement

We declare that there are no conflicts of interest that could be perceived as prejudicing the impartiality of this research.

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Author Contributions

C.S., J.S.M., H.P., M.J.B. were involved in the acquisition and treatment of data. M.J.B. also participated in critically revising the manuscript and giving the final approval of the version to be published. All authors read and approved the final manuscript.

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