

Usefulness of preoperative serum calcitonin in patients with nodular thyroid disease without suspicious history or cytology for medullary thyroid carcinoma

Utilidade da calcitonina sérica pré-operatória em pacientes com doença nodular tireoidiana sem história ou citologia suspeitas para carcinoma medular de tireoide

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ABSTRACT

Objective: To evaluate the usefulness of preoperative serum calcitonin (sCT) in patients with nodular disease without suspicion of medullary thyroid carcinoma (MTC) in history or cytology. **Patients and methods:** sCT was measured before thyroidectomy in 494 patients with nodular disease who had no family history of MTC or multiple endocrine neoplasia type 2, and no cytological suspicion of MTC. **Results:** Basal sCT was < 10 ng/mL in 482 patients and none of them had MTC. One patient with basal sCT > 100 pg/mL had MTC. Among the 11 patients with basal sCT between 10 and 100 pg/mL, MTC was diagnosed in only one. The two patients with MTC were submitted to total thyroidectomy, combined with elective lymph node dissection indicated exclusively based on hypercalcitoninemia, and sCT was undetectable after six months. **Conclusions:** Preoperative sCT is useful for the detection of sporadic MTC in patients with nodular disease, even in the absence of suspicious history or cytology. *Arq Bras Endocrinol Metab.* 2013;57(4):312-6

Keywords

Calcitonin; medullary carcinoma; nodular disease

RESUMO

Objetivo: Avaliar a utilidade da calcitonina sérica (sCT) pré-operatória em pacientes com doença nodular sem suspeita de carcinoma medular de tireoide (CMT) pela história e citologia. **Pacientes e métodos:** Antes da tireoidectomia, sCT foi dosada em 494 pacientes com doença nodular, sem história familiar de CMT ou neoplasia endócrina múltipla tipo 2 e sem citologia suspeita para CMT. **Resultados:** sCT basal foi < 10 ng/ml em 482 pacientes e nenhum possuía CMT. Um paciente com sCT basal > 100 pg/ml realmente possuía CMT. Dos 11 pacientes com sCT basal entre 10 e 100 pg/ml, CMT foi diagnosticado em apenas um. Os dois pacientes com CMT foram submetidos à tireoidectomia total com dissecação eletiva de linfonodos, indicada exclusivamente pela hipercalcitoninemia, e após seis meses apresentaram sCT indetectável. **Conclusões:** Em pacientes com doença nodular, mesmo sem história ou citologia suspeitas, a sCT pré-operatória é útil para detecção do CMT esporádico. *Arq Bras Endocrinol Metab.* 2013;57(4):312-6

Descritores

Calcitonina; carcinoma medular; doença nodular

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INTRODUCTION

There is consensus regarding the usefulness of serum calcitonin (sCT) in patients with nodular disease and family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia type 2 (MEN-2) (1-3), or with suspicious cytology for MTC (4). Controversy exists in cases without suspicious history or cytology, with some authors defending routine measurement of sCT (1), whereas others consider the evidence to be insufficient for this recommendation (2,5).

In the case of patients with an indication for thyroidectomy, irrespective of sCT, the finding of hypercalcitoninemia modifies the extent of the procedure (to total thyroidectomy with elective dissection of cervical lymph nodes). This approach enables effective treatment of MTC already in the first intervention, without the need for surgical reintervention, which might be necessary when histology reveals this tumor and the first surgery was less extensive (4).

However, the cost of sCT measurement (basal and after stimulation in some cases), which needs to be performed in hundreds of patients in order to detect one case of MTC exclusively by this method, and the risk of false-positive results are limitations of routine preoperative sCT measurement in patients without suspicious history or cytology.

The different positions on this topic in current guidelines (1-3,5) clearly demonstrate that more studies are desirable. The objective of the present investigation was to evaluate the usefulness of sCT in patients with nodular thyroid disease and indication for surgical treatment, and who had no suspicion of MTC in history or cytology.

PATIENTS AND METHODS

Design

Prospective study

Patients

First, patients with nodular thyroid disease and an indication for surgery were evaluated. In these cases, the decision for surgery was made before sCT measurement and, therefore, was not influenced by this result. The following patients were excluded: (i) those with a family history of MTC or MEN-2; (ii) those with suspicious cytology or diagnosis of MTC; (iii) and those with known kidney failure, hyperparathyroidism, chronic atrophic gastritis, neuroendocrine tumor, or pulmonary carcinoma.

Only patients whose indication for surgery was in accordance with current guidelines were included (1-3,5).

Measurement of serum calcitonin and management of the patients

For the measurement of sCT performed 30 days or less before thyroidectomy, patients were asked not to consume alcoholic beverages for at least 1 week, and not to use proton pump inhibitors for at least 4 weeks. At the time of measurement, none of the patients had bacterial infections or hypercalcemia.

Patients with basal sCT > 10 pg/mL underwent a calcium stimulation test [rapid venous infusion of 2.5 mg calcium/kg in the form of 10% calcium gluconate (10 ml/min)]. Serum calcitonin was measured before and 2, 5 and 10 min after the infusion of calcium. Patients with stimulated sCT > 100 pg/mL were submitted to total thyroidectomy combined with elective dissection of the cervical lymph nodes (indicated exclusively based on the finding of hypercalcitoninemia).

The study was approved by the local Research Ethics Committee.

Assay

Serum calcitonin was measured by an immunochemiluminescent assay (Immulite, Diagnostic Products Corporation, Los Angeles, CA, USA). The sensitivity of the assay was 2 pg/mL.

Fine-needle aspiration biopsy

Fine-needle aspiration biopsy (FNAB) as performed with a 22-gauge needle and a 5- or 10-mL syringe and guided by ultrasound. The smears were analyzed by pathologists experienced in thyroid pathology.

RESULTS

A total of 494 patients (374 women and 120 men), ranging in age from 12 to 85 years (median: 50 years), were studied. Cytology results are shown in table 1. One hundred and twenty-four patients were submitted to partial thyroidectomy (euthyroid patients with unilateral nodular disease and no cytological suspicion of malignancy), and 370 patients were submitted to total thyroidectomy, with cervical lymph node dissection in 65 (62 because of papillary carcinoma cytology and a suspicion of metastasis during the perioperative period and 3 exclusively because of the finding of hypercalcitoninemia).

Table 1. Results of cytology in the patients studied

Cytology	N
Benign	98
Insufficient (in two ultrasound-guided punctures)	69
Follicular lesion or atypia of undetermined significance (in two punctures)	80
Follicular neoplasm or suspicion of follicular neoplasm	82
Suspicion of malignancy or malignant (except for medullary thyroid carcinoma)	165

Basal sCT was < 10 ng/mL in 482 patients. MTC was not detected in any of these cases. Serum calcitonin was > 100 pg/mL in only one patient and histology confirmed MTC in this case. Finally, 11 patients had basal sCT > 10 ng/mL, but < 100 pg/mL. Histology revealed MTC in one of these patients (the only case with basal sCT > 50 pg/mL). Ten patients with basal sCT > 10 ng/mL (< 50 pg/mL) did not have MTC, and only one of these patients presented stimulated CT > 100 pg/mL. Three patients were submitted to partial thyroidectomy. In these cases, MTC in the remnant gland was ruled out by the absence of nodules in post-operative ultrasound scans and a reduction of basal CT to levels < 5 ng/mL six months after surgery. Data of the patients with basal sCT > 10 pg/mL are shown in table 2.

The two patients with MTC were submitted to total thyroidectomy and elective dissection of the cervical lymph nodes. Micrometastases were detected in two lymph nodes of one of these patients. The tumors measured 7 and 12 mm, and the initial stages were

T1aN0M0 and T1bN1aM0, respectively. Basal sCT was undetectable in the two patients 6 months after the initial surgery.

DISCUSSION

This study included only patients without a suspicion of MTC in history and cytology. In fact, there is consensus regarding the usefulness of sCT in patients with family history of MTC or MEN-2 (1-3), or those with suspicious cytology for this cancer (4). Cytology result of MTC may be interpreted as papillary carcinoma, indeterminate, or even benign (6-8). In addition, in subjects who are at low clinical risk for malignancy, only nodules ≥ 1 cm are submitted to FNAB (5), and an eventual microcarcinoma associated with macronodules may therefore not be detected. These arguments favor the measurement of sCT even in patients who already underwent FNAB and whose cytology result is not suggestive of MTC.

We evaluated only patients with surgical indication, irrespective of sCT. In these cases, the finding of hypercalcitoninemia modifies the extent of the procedure, enabling adequate treatment of possible MTC already in the first intervention. In fact, two cases of MTC diagnosed by preoperative sCT were submitted to total thyroidectomy and elective cervical lymph node dissection exclusively based on the finding of hypercalcitoninemia, which led to complete biochemical remission. Specifically in this situation (measurement of sCT

Table 2. Data of patients with basal serum calcitonin > 10 pg/mL

Gender	Age (years)	Cytology	Frozen section	Basal sCT (pg/mL)	Stimulated sCT (pg/mL)	Surgery	Histology
F	78	Benign	NA	20	42	TT	CG
F	50	Benign	NA	25	56	TT	CG
M	75	Insufficient	NA	12	38	PT	CG
F	16	Follicular lesion of undetermined significance	NA	18	45	PT	PTC
M	50	Atypia of undetermined significance	Benign	32	75	TT	HT
F	46	Follicular neoplasm	NA	112	887	TT + ND	MTC
F	62	Follicular neoplasm	NA	23	40	PT	FA
F	53	Suspicion of PTC	Malignancy	56	216	TT + ND	MTC
F	72	Suspicion of PTC	Malignancy	21	40	TT	PTC
F	29	PTC	NA	16	31	TT	PTC
M	42	PTC	NA	30	108	TT + ND	PTC + CCH
F	18	PTC	NA	25	43	TT	PTC

in patients with surgical indication), the frequency of MTC was 0.4% in the present study. Two other series reported a frequency of 0.5% (9) and 1.37% (10).

Another matter of discussion are the cutoff values of sCT. Whereas sporadic MTC is very unlikely in the presence of basal sCT < 10 pg/mL (9,10), serum concentration > 100 pg/mL has an excellent positive predictive value (PPV) for this tumor in the absence of any apparent cause (*e.g.*, chronic renal failure, use of proton pump inhibitors, other known secretory tumors) (6,8-21), and stimulation tests are not necessary in these cases. Despite the traditional cutoff value of 100 pg/mL, at least in women, PPV of 100% was reported in many series for basal sCT > 60 pg/mL (6,8-10,12-14,17-21). In agreement with this finding, in the present study, after known causes of hypercalcitoninemia were excluded, none of the 492 patients without MTC had basal sCT > 40 pg/mL.

In patients in whom a stimulation test is indicated (intermediate basal sCT levels), stimulated sCT < 100 pg/mL also renders sporadic MTC unlikely. In contrast, PPV of stimulated sCT > 100 pg/mL is controversial. Although some studies reported PPV of 100% (8,10,20), many series found a value of only 25% (21), 20% (22), and 0/13 (9) in patients with elevated basal sCT, but < 100 pg/mL, who converted to levels > 100 pg/mL after stimulation. As a consequence, different cutoffs of stimulated sCT have been proposed in the literature (11-13,15,19), and this value remains undefined.

In countries such as Brazil where pentagastrin is not readily available, although its importation is possible, calcium can be used for stimulation tests. In addition to being a known stimulus of CT secretion and showing an excellent correlation with post-pentagastrin peak, calcium is better tolerated (13,23). In the present study, all 11 patients with basal sCT between 10 and 100 pg/mL received venous infusion of calcium for the stimulation test. Two of these patients presented stimulated sCT > 100 pg/mL, one had MTC and the other had C-cell hyperplasia.

Finally, the strengths of the present study are its prospective design; the fact that cytology was available for all patients; the stimulation test using calcium, and the fact of being the largest Brazilian series evaluating measurement of sCT as a screening method for sporadic MTC.

We conclude that preoperative measurement of sCT is useful for the detection of sporadic MTC in patients

with nodular thyroid disease, even those without suspicious history or cytology for MTC, enabling adequate surgical treatment of this cancer already in the first intervention. In cases in which basal sCT does not elucidate the case, the calcium stimulation test seems to be of value for the identification of patients with MTC.

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