

# Simultaneous medullary carcinoma and differentiated thyroid cancer



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## Case report

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### Simultaneous medullary carcinoma and differentiated thyroid cancer. Case report

**BACKGROUND:** Medullary thyroid cancer (MTC) is an uncommon and aggressive tumour representing only 5-10% of all thyroid malignancies. MTC arises from parafollicular thyroid cells (C-cells) producing calcitonin hormone.

Differentiated thyroid cancer (DTC) is the most frequent thyroid tumour (papillary or follicular), representing 80% of all thyroid cancer. DTC derives from follicular thyroid cells, that come from the central thyroid sketch. The association between medullary and papillary thyroid cancer is rare. Several cases have been reported of mixed carcinomas.

**CASE REPORT:** We report two cases of associated medullary and papillary carcinomas in two different foci in patients with respectively Graves' disease and multinodular goiter. A young woman affected by Grave's disease and multinodular goiter under pharmacological treatment with antithyroidal drugs underwent total thyroidectomy. The histopathological examination revealed the presence of a medullary carcinoma of the middle third of right lobe (1.1 cm) with an adjacent papillary microcarcinoma (0.5 cm). A 72-years-old woman, affected by euthyroid multinodular goiter, underwent total thyroidectomy. The pathological findings were two microcarcinomas, medullary (0.44 cm) in the left lobe and papillary (0.22 cm) in the right lobe.

**CONCLUSION:** We can speculate that this coexistence is inferred, not having shown a specific cause that justifies the association between the two types of tumour and the high prevalence of papillary carcinoma.

**KEY WORDS:** Medullary, Papillary, Thyroid carcinoma.

### Introduction

Medullary thyroid cancer (MTC) is an uncommon tumour representing only 5-10% of all thyroid malignancies; it is sporadic in 80% of cases and genetically determined in 20%. The latter ones can be associated with other endocrinopathies including pheochromocytoma and hyperparathyroidism in the multiple endocrine neoplasia syndromes (MEN IIa and MEN IIb). Familial medullary thyroid carcinoma (FMTC) is a rare form not

associated with any other endocrinopathies. The genetic basis for these familial tumours derives from a series of missense germline mutations in the RET proto-oncogene. Genetic testing by DNA analysis facilitates identification of family members at risk who can now be offered early "prophylactic thyroidectomy" with an increased prospect of surgical success and long-term survival.

MTC arises from parafollicular thyroid cells (C-cells) producing calcitonin hormone that migrate from the third and fourth branchial pouch to the lateral thyroid sketches. The middle third of thyroid lobe, actually, is the most common site of MTC.

The principal feature of MTC is calcitonin production, that's why this peptide is considered the most important marker of this tumour<sup>1</sup>. Nevertheless, MTC produces other hormones like CGRP (Calcitonin-gene related pep-

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tide), chromogranine, CEA, amyloid, ACTH, VIP (Vasoactive Intestinal Peptide) and PG. MTC is an aggressive malignancy and gives early metastases to neck nodes.

Differentiated thyroid cancers (DTC) is the most frequent thyroid tumour (papillary or follicular), representing 80% of all thyroid cancer. DTC derives from follicular thyroid cells, that come from the central thyroid sketch.

The association between medullary and papillary thyroid cancer is rare. A few cases are present in literature. We report two cases of associated medullary and papillary carcinomas in patients with respectively Graves' disease and multinodular goiter.

## Case report

We report two cases of simultaneous incidental association of medullary and papillary thyroid carcinoma.

**Case A.** A young woman (35-years-old) affected by Grave's disease and multinodular goiter under pharmacological treatment with antithyroidal drugs (methimazole) underwent total thyroidectomy. She had a family history of multinodular goiter and a history of bilateral breast cysts. Preoperative blood exams were within the normal limits, except for autoantibodies (TgAb, TPOAb and TrAb). Neck ultrasonography showed two nodules at the left lobe and three at the right lobe. Two of the right thyroid nodules showed IIIb vascularization and had irregular margins. One of these (0.5 cm) had microcalcifications in its contest. There were no detectable lymphnodes.

The histopathological examination revealed the presence of a medullary carcinoma (Fig. 1) of the middle third of right lobe (1.1 cm) with an adjacent papillary microcarcinoma (0.5 cm) (Fig. 2). C-cell hyperplasia was absent. Immunohistochemical examination showed positive cellular expression for calcitonin (Fig. 3), chromogranine and CEA; it was negative for thyroglobulin and S100.

**Case B.** A 72-years-old woman, affected by euthyroid multinodular goiter, underwent total thyroidectomy. She suffered from chronic C hepatitis and hiatal hernia; she also had a history of tubercular mesenteritis. Pre-operative ultrasonography showed several thyroid nodules and no detectable cervical lymphnodes.

The histopathological examination revealed two microcarcinomas, medullary (0.44 cm) in the left lobe (Fig. 4) and papillary (0.22 cm) in the right lobe (Fig. 5). C-cell hyperplasia was absent. Immunohistochemical examination showed positive cellular expression for calcitonin (Fig. 6), chromogranine and CEA and negative cellular expression for thyroglobulin and S100.

We had a pre-operative diagnosis of Graves' disease concomitant with multinodular goiter in the first case and

euthyroid multinodular goiter in case B. Consequently, the choice surgical procedure was total thyroidectomy. Blood calcitonin wasn't measured before surgery, so pre-operative suspect of medullary carcinoma didn't exist. Screening for RET gene mutations<sup>4,5</sup> was performed in the post-operative period. It was negative in both patients for on the analysis of the most common involved exons. So we can classify these two medullary carcinoma as sporadic ones.

One year follow-up showed no thyroid remnants or metastatic nodes. Laboratory exams which comprised TSH, FT3, FT4, TG, CT, CEA, calcaemia, fosoremia, serum protidogram and pentagastrin test were negative in case A. In case B, instead, there was a wild positivity of pentagastrin test, without ultrasonographic signs of recurrence, except for one cervical lymphatic node measuring 10 x 8 mm. Because of its dimensions and its deep position near jujular vein, fine-needle aspiration with cytology, thyroglobulin and calcitonin measurement in the needle washout couldn't be performed.

## Discussion

Papillary carcinoma (PTC) represents the most common thyroid malignancy. It belongs to differentiated thyroid carcinoma and arises from thyrocytes (follicular epithelial cells) that produce thyroglobulin and thyroid hormones. PTC is the less aggressive histological type and the 10-year survival rate is about 93%. Age is the most important prognostic factor. Patients less than 45-years old, actually, have a better outcome compared to older ones. Some PTC histological variants are at higher risk (nodular and diffuse follicular, high cells, columnar cells). Microcarcinoma is a tumour measuring one centimeter or less. DTC therapy found in 131 a valid aid to surgery. Medullary carcinoma arises from parafollicular C cells secreting calcitonin and deriving from neural crests. It represents a peculiar histological type both for its embryological origin that for its frequent association with MEN2. MTC is a rare (5-8 % of thyroid malignancies) and aggressive malignancy, with a high tendency to lymphatic and blood spread (to bone, liver and lungs). Unlike PTC, MTC is a tumour which does not take up radioactive iodine, is relatively radioresistant and poorly responsive to chemotherapy. Therefore, surgery is the only treatment which can offer the prospect of cure. Several cases have been reported of mixed carcinomas showing features of both tumour in the same lesion (medullary and papillary/follicular)<sup>2</sup>. Most rarely we found association of these histological types in two different *foci* separated by non-neoplastic thyroid parenchyma.

In the two cases described above medullary carcinoma (or microcarcinoma), cancer has proved to be sporadic, without RET mutations<sup>6</sup>. Patients with sporadic MTC may have a less favourable prognosis than FMTC and

MEN IIa although the earlier diagnosis of hereditary cases by biochemical screening and mutational analysis may be a significant factor influencing the comparison <sup>7</sup>.

Both tumours were found incidentally after total thyroidectomy performed for multinodular goiter. Pre-operative diagnosis of medullary carcinoma, actually, would have predicted the central neck compartment dissection, especially in sporadic tumours. Both lateral nodal dissection should be performed if central compartment nodes are detectable by ultrasound or intra-operatively. In our cases central compartment dissection was not performed after first surgery on endocrinologist advice, because 1-year follow-up didn't show any recurrence sign. Moreover, some Authors <sup>8</sup> proposed that complete total thyroidectomy and neck dissection might not be necessary when a small pT1 tumour is incidentally identified by postoperative histology of a thyroid gland removed for other reasons, providing hereditary disease is excluded by DNA analysis.

Several hypotheses have been made to explain the association of MTC with PTC. A common embryological origin of follicular epithelial and parafollicular cells from a single stem cell has been suggested, with subsequent differentiation; notwithstanding this theory would only explain the development of tumours with histological features common to both types (mixed tumours).

Coexistence of two different malignancies, the so-called "collision tumours" could be due to a common tumorigenicity in patients with a history of neck radiation exposure. This history, however, is not non so common as in the past decades so it can't be invoked as a cause of death. This hypothesis is not confirmed genetic studies <sup>3</sup>, that indicate, for the first time, a different genetic origin of the two coexisting neoplasms.

We can speculate that this coexistence is inferred, not having shown a specific cause that justifies the association between the two types of tumour, however very rare, and the high prevalence of papillary carcinoma, even in autopsy studies <sup>3</sup>. It is tempting, however, to speculate that these coexisting neoplasms arise in thyroid glands rendered more prone to various genetic events by still unknown mechanisms.

## Conclusions

Medullary carcinoma is a rare and aggressive thyroid malignancy. We report two cases of MTC associated with papillary carcinoma just incidentally encountered after total thyroidectomy performed for benign disease. It's important to know pre-operative diagnosis of medullary carcinoma to better plan surgery, that's the only effective therapy for this tumour and will involve central neck nodes dissection. As MTC occurs in 0.6% of thyroid nodules <sup>8</sup>, all patients undergoing assessment for nodular thyroid disease should have at least basal calcitonin measurement in order to avoid the undesirable surprise

of the incidentally discovered MTC<sup>18</sup>. However, an elevated calcitonin level does not always indicate MTC and cannot distinguish between C-cell hyperplasia and tumour especially when only mildly raised. In the two cases that we reported central neck compartment dissection was not performed in a second look because, during 1-year follow-up, no clinical, microscopic and ultrasonographic sign of persistence or recurrence was found.

## Riassunto

Il carcinoma midollare tiroideo (MTC) deriva dalle cellule parafollicolari tiroidee (cellule C) secernenti calcitonina e rappresenta il 5-10% di tutti i tumori tiroidei ed è sporadico nell'80% dei casi e familiare nel 20% (FCMT o MEN2). La principale caratteristica del CMT è la produzione di calcitonina, motivo per cui questo peptide è considerato il più importante marker di tale tumore.

Il carcinoma differenziato tiroideo (DTC) è il tumore tiroideo più frequente (papillifero o follicolare), rappresentando l'80% di tutti i tumori tiroidei. Il DTC deriva dalle cellule follicolari tiroidee, appartenenti all'abozzo tiroideo mediano. L'associazione tra carcinoma tiroideo midollare e follicolare è rara. Solo pochi casi sono riportati in letteratura.

Nel presente studio riportiamo due casi di associazione incidentale di carcinoma tiroideo papillifero e midollare.

**Caso A.** Una giovane donna affetta da malattia di Grave's e gozzo plurinodulare in trattamento farmacologico con antitiroidei fu sottoposta a tiroidectomia totale. L'esame istologico mostrò la presenza di un carcinoma midollare (1.1 cm) con adiacente un microcarcinoma papillifero (0.5 cm).

**Caso B.** Un'altra donna, affetta da gozzo plurinodulare eutiroideo, fu sottoposta a tiroidectomia totale. L'esame istologico dimostrò la presenza di due microcarcinomi, midollare (0.44 cm) a carico del lobo sinistro e papillifero (0.22 cm) nel lobo destro.

In entrambi i casi era assente iperplasia delle cellule C. L'immunoistochimica era positiva per calcitonina (Fig. 6), cromogranina e CEA e negativa per tireoglobulina ed S100. Il test di screening per mutazioni del proto oncogene RET era negativo in entrambe le pazienti, dimostrando la sporadicità dei due tumori.

Il follow-up ad un anno non ha mostrato segni di persistenza o recidiva di malattia, eccetto che nel caso B in cui è stato rilevato ecograficamente un linfonodo iuxtavaginale che, per le piccole dimensioni e per la posizione iuxtavasale, non è stato sottoposto ad FNA con dosaggio della calcitonina sul liquido di lavaggio.

In letteratura sono stati riportati parecchi casi di carcinomi misti che mostravano nella stessa lesione caratteristiche proprie del carcinoma midollare e di quello papil-

lifero. Più rara è, invece, l'associazione dei due tipi di tumore in foci separati, come nei due casi sopra citati. Entrambi i tumori sono stati un riscontro occasionale dopo tiroidectomia totale eseguita per altre indicazioni. Non essendosi dimostrata una causa specifica che giustifichi l'associazione tra i due tipi di tumore, si può ipotizzare che tale coesistenza sia puramente casuale.

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