# Mixed Medullary – Papillary Thyroid Carcinoma with mixed lymph node metastases: a case report

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**Key Clinical Message**: Mixed medullary-follicular-derived carcinoma is a very rare event in clinical practice. It is extremely important to make the correct diagnosis, on account of the prognostic and treatment implications. A genetic study of these patients is advisable.

## Abstract

Medullary and papillary thyroid carcinoma are two distinct neoplasms. Its simultaneous is uncommon and its occurrence as a mixed follicular medullary carcinomas is extremely rare. We present a 60-year-old man with the mixed medullary-papillary carcinoma of the thyroid and papillary and medullary component metastases on lymph nodes.

## Introduction

Papillary thyroid carcinoma (PTC) is the most common (approximately 85%) thyroid carcinoma and is derived from thyroid follicular cells of the endoderm (1). In contrast, medullary thyroid carcinoma (MTC) is an uncommon malignant epithelial neoplasm [5-10% of all thyroid cancers (2)] which originates from the parafollicular C-cell, which is traditionally assumed to evolve from the ultimobranchial body of the neural crest (3). The cell origin, histopathologic features, and prognosis of these tumors are different and the simultaneous occurrence of these tumors is a rare event (4-10). Indeed, they can occur in the same patient as a collision tumor or as mixed medullary-follicular thyroid carcinoma (MMFTC) (a real mixed tumor, with the immunoreactivity and morphological features of both carcinomas) (11).

We present a case report of this rare association and provide a short review of the literature of this rare condition.

## Case Report

The patient in question was a 60-year-old man with a history of atrial fibrillation (which was diagnosed in 2015), associated with amiodarone induced thyrotoxicosis. An evaluation was thus made of the thyroid gland. The thyroid was palpable during a neck examination, without the detection of thyroid nodules or cervical adenopathies. An ultrasound examination of the neck showed a 22mm (the largest dimension) solid nodule on the left thyroid lobe (on a multinodular thyroid gland), with irregular margins and microcalcifications; supraclavicular suspicious adenopathy was also noticed.

The patient underwent fine needle aspiration (FNA) cytology in another hospital, which suggested the possibility of medullary thyroid carcinoma with supraclavicular lymph node metastasis. The patient was then referred to our hospital for additional investigations and surgical treatment. There were no other physical abnormalities. He had no history of prior radiation therapy and his family history was negative for thyroid cancer and other endocrinopathies.

Serum calcitonin was elevated (428.5pg/mL; NL: <14.3pg/mL), with normal urinary normetanephrines and metanephrines. Preoperative levels of TSH (1.90 mU/L) and free T4 (0.963 ng/dL) were normal, even without any medication for the thyroid function (after suspension of amiodarone). He also had a normal serum level of calcium, phosphorus, and parathyroid hormone.

A total thyroidectomy with bilateral cervical lymph node dissection (Levels II to VII) was performed. The thyroid gland weighed 35.3g, with a bosselated surface. A white/tan nodule, which was poorly circumscribed, with 2.3 x 1.5 x 1.2cm was identified in the middle third of the left lobe. A second nodule with similar characteristics was observed on the lower pole of the left lobe, measuring 1.9 x 1cm. The dissected soft tissue from the neck was carefully examined for lymph nodes, and each region was separately sampled. 68 lymph nodes were isolated, the largest being 2.6 cm.

On microscopic examination, the tumor had 23mm of the largest dimension and was composed of two components which were intimately intermingled. In one of these components the cells had PTC characteristics with strongly and uniformly positive staining for thyroglobulin, and negative for calcitonin (figure 1A, 2). The other component showed characteristics which are consistent with medullary thyroid carcinoma, with strong immunoreactivity to calcitonin, synaptophysin, Chromogranin A, and which are negative for thyroglobulin (Figure 1B, 3). Vascular invasion was present. Limited extra-thyroid extension was also observed, but with no involvement of striated muscle tissue. A 1mm papillary microcarcinoma was concurrently observed in the right lobe. Eight out of ten isolated central lymph nodes had metastases from both components (the largest with 14mm), as well as 12 out of 38 of the left lymph nodes (the largest with 20 mm). A final diagnosis identified a mixed medullary-papillary carcinoma of the thyroid and the patient accordingly underwent ablative treatment with $I^{131}$. As a medullary thyroid carcinoma can be associated with hereditary syndromes, such as MEN2, a mutational analysis was performed to investigate the presence of RET germline mutations, which was negative.

Serum levels of calcitonin returned back to normal after the surgical procedure and are currently stable (calcitonin: 0.800pg/mL; non-detectable levels of thyroglobulin and of anti-thyroglobulin antibodies, with normal thyroid function). During a subsequent ultrasound examination of the neck, signs of lateral cervical emptying were observed, with some cervical lymph nodes having no pathological morph-dimensional criteria. The largest was 8mm long and was situated in the 1/3 lower-right carotid jugular chain, showing an eccentric adipose hilum with hilar Doppler flow, which was referred for ultrasound surveillance. The patient is currently undergoing substitution therapy and is clinically well one year after surgery.

## Discussion

The occurrence of medullary thyroid carcinoma, together with papillary carcinomas, forming a mixed tumor is very rare, although it has been reported in the past (8).

Medullary thyroid carcinoma was first described by Hazard et al., in 1959, in a patient with thyroid carcinoma with solid, non-follicular structure with amyloid in the stroma (12). In 1979 follicular structures between cells with typical medullary features was described (13). Subsequently, detectable thyroglobulin in the foci with follicular appearance in such atypical MTCs has been shown and it was proposed that these tumors could represent a new disease, which was named "mixed medullary-follicular carcinoma" (MMFC) (14, 15). Mixed medullary-follicular carcinoma was defined as a distinct entity, being classified by the World Health Organization (WHO) in 1988 (16) as "tumors which show the morphological features of both a medullary carcinoma with immunoreactivity for calcitonin and a follicular carcinoma with immunoreactivity for thyroglobulin". This condition is different from the existence of MTCs with follicles (17) or papillae (18), as well as from MTCs with normal follicles which are entrapped within the tumor. Later, in 2004 (19), high rates of simultaneous PTC (13.8%) in patients with MTC were reported, in similarity to 2010, when Kim *et al*

identified the presence of PTC in 19% of patients with MTC (20), however, the true mixed nature of these tumors remains a rare entity (8).

The etiology of this mixed tumor is not well understood, although several theories have been proposed. One possibility is that tumor could arise from a common progenitor cell (21), maybe in the ultimobranchial rests, with subsequent divergent differentiation in parafollicular and follicular cell lines; another explanation is the presence of a common tumorigenic stimulus (such as radiation exposure) which promotes the oncogenic transformation of both cells types (22). Some suggest a potential role for RET germline mutations in the development of both tumor types, however the genetic analysis of RET oncogene in this type of tumor leads to conflicting results (23, 24). Another possible, and more plausible, theory is ‘‘hostage hypothesis’’, where the malignant transformation of C cells, with entrapment of normal follicles leads to a microenvironment which subsequently stimulates the neoplastic development of the trapped follicular cells (25).

Of note, is the atypical presentation of this rare carcinoma in our patient with hyperthyroidism, which is not considered one of the primary symptoms of thyroid cancer (26). The association between thyrotoxicosis and thyroid cancer is rare and little-recognised, which can lead to a delay in diagnosis, and, consequently, to a worse prognosis. However, there an increasing number of studies have demonstrated that this association is possible and that a careful assessment of the thyroid gland is essential whenever any thyroid dysfunction is detected (26). With regard to amiodarone treatment, even if amiodarone-induced thyrotoxicosis (AIT) is a well-known complication of this drug (27) – which is found in 3% to 12% of patients – the presence of thyroid cancer in thyroidectomy specimens removed for AIT is also rare (28, 29), (30-32). Two main types of AIT have been described: type 1 AIT – iodine-induced hyperthyroidism, which often occurs with a background of pre-existing thyroid disease; type 2 AIT – due to destructive thyroiditis in a normal thyroid gland (27). Although the patient was evaluated by another hospital for AIT and we have few details regarding its etiological assessment and approach, in recent years, several case reports have raised the possibility of an association between amiodarone and cancer (33, 34). Thyroid dysfunction resulting from this drug can either be induced in patients with previous thyroid carcinoma (35) or can occur after the introduction of this drug (29). With regards our patient: could amiodarone have induced the neoplastic transformation of pre-existing nodules? Could AIT arise on account of the presence of an underlying, previously-unknown, thyroid cancer? We don't know for sure, but this case highlights the importance of a detailed assessment of the thyroid gland which is not only analytical, but is also subject to an ultrasound in a patient who is taking amiodarone.

The most commonly-reported presentation of MMFTC is a gradually increasing neck swelling (36-38). In most cases, lymph node metastases were reported at diagnosis, as a single tumor cell population, or, alternatively, as a mixture of both components within the same lymph node (38-40). Foci consistent with mixed medullary and papillary carcinoma were observed in our case, and immune-histo-chemical findings which support both types of carcinoma were detected in these foci.

Mixed medullary-follicular thyroid carcinoma is more frequent in middle-aged patients, with serum calcitonin level being high in almost all cases (9, 38), such as in our patient. Tumor size is variable and is generally unifocal (25). Multifocal tumors are more frequent in patients with MEN 2A (5).

Although the FNA cytology of the thyroid nodule had suggested the possibility of medullary thyroid carcinoma, a microscopic evaluation was observed of follicular structures with nuclear papillary features, which highlights the importance of the complete histological tumor evaluation, as FNA is a sensitive initial examination but may not be representative of the total tumor area.

Treatment of mixed medullary-follicular thyroid carcinoma is mainly driven by the medullary component. However, this type of tumor treatment remains controversial (25), not only due to the few reported cases, but also to the use of different treatments in the reported cases. Surgery (including of the tumor and areas of lymphatic drainage - Levels II to VII) is accepted as the first-choice (41). The role of adjuvant therapies (radioiodine and chemotherapy) remains controversial. Maybe this is due to the major part of the tumors being of medullary origin, although there is no conclusive evidence regarding the efficacy of adjuvant radioiodine treatment. However, as these tumors have thyroglobulin immune-reactive cells, the possible efficacy of this therapy was suggested at least on the follicular component (38, 42). Our patient had abnormally elevated levels of calcitonin at the time of diagnosis and was treated initially with surgery and also underwent ablative treatment with I131, due to papillary component.

In the follow up, blood calcitonin and thyroglobulin levels could be helpful to guide the therapeutic approach. Our patient is stable and under surveillance.

A recent study investigated 183 patients with simultaneous PTC-MTC. 45% of these patients were disease-free after >10 years from diagnosis, with prognosis being determined mainly by the medullary component of the tumor (4). Measurement of calcitonin in the pre-surgical work-up of thyroid nodules with positive cytology for PTC has also been advocated to aid in the early diagnosis of concomitant MTC. Although the guidelines consider that there is no clear evidence in favour of the measurement of serum calcitonin in the pre-operatory period of patients with thyroid nodules (43), if the FNA of our patient had only detected the papillary component of the tumor, then the measurement of this marker could have led to a correct diagnosis, that would remain hidden until the patient was submitted to surgical resection.

A precise and early diagnosis of this uncommon variety of thyroid carcinoma is essential for both the adequate treatment of the patient and also the genetic screening (to exclude MEN2 syndromes and familial medullary thyroid carcinoma – FMTC). The role of FNA cytology in the diagnosis of these type of tumors is limited and could lead to misdiagnosis, for it is fundamental to correlate the cytological diagnosis with serum calcitonin levels and also to confirm the diagnosis in the immune-histochemical investigation of the surgical specimen.

## Conclusion

This paper describes an atypical presentation of an extremely rare type of tumor in clinical practice, highlighting the importance of an adequate assessment of the thyroid gland in the presence of any type of thyroid dysfunction, as well as the measurement of pre-operative calcitonin levels, the complete histological examination (morphological and immunohistochemical), and also lymph node dissection with a careful search for metastatic disease (due to the presence of many metastases in the bilateral cervical lymph node).

## Statements


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### Conflict of interest

The authors declare that they have no conflict of interest.

### Author contribution

VG: wrote this case report and. CC, JO, APS, MJ, PF and DC: revised the draft. MF: helped in the writing of this case report. IT: was involved in the patient care and revised the draft.

### Patient consent

Written informed consent has been obtained from the patient.


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**List of figures:**