Mixed Medullary Papillary Thyroid Carcinoma in Hyperfunctioning Hot Nodule: A Case Report and Review of the Literature

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Abstract: Mixed medullary papillary carcinoma (MMPC) is a rare variant of papillary thyroid carcinoma, according to the WHO classification and it presents as a single lesion histologically composed of two distinct and intermingled neoplastic cell patterns. The histogenesis is still debatable. The lymph node metastases are usually present at the time of the diagnosis and distal metastases may appear late during follow-up. At least 13 similar lesions have been reported in the literature. We describe the case of a 61-year-old woman with a mixed medullary papillary carcinoma found in a hyperfunctioning thyroid nodule and negative pre-surgical serum calcitonin. After surgery, the patient started suppressive L-thyroxine therapy and underwent radioiodine ablation. The follow-up for both papillary and medullary components has shown no signs of persistence or recurrence of disease five years after surgery.

However, the rarity of the MMPCs makes the management and the prognosis of these tumors still unclear.

Keywords: Mixed medullary papillary carcinoma, calcitonin, hyperfunctioning thyroid nodule, thyroid ultrasound, fine needle aspiration, thyroidectomy.

INTRODUCTION

Papillary thyroid carcinoma (PTC) and medullary thyroid carcinoma (MTC) differ in terms of incidence, cell origin, histopathological features, treatment and follow-up.

Simultaneous occurrence of MTC and PTC in the same thyroid is uncommon, being less than 1% of all thyroid malignancies [1] and can be observed in two main settings: a *mixed tumor*, a single lesion showing dual differentiation and a *collision tumor*, with PTC and MTC foci detected in different parts of the gland and separated by normal thyroid tissue. The latter type of tumor is defined as mixed medullary papillary carcinoma (MMPC), a rare variant of " papillary thyroid carcinoma", according to the WHO classification [2,3].

We report a case of mixed medullary papillary carcinoma in a hyperfunctioning nodule, illustrating the challenging treatment and follow-up of this tumor and we review the literature.

CASE REPORT

A 61-year-old woman with a toxic multinodular goiter was referred to our unit for progressive dysphagia and respiratory distress in November 2008. Her family history was negative for thyroid and other endocrine tumors. The patient had no history of neck or whole body irradiation. Physical examination of the neck revealed a left well-demarcated mass moving up on swallowing. The patient was on thiamazol since November 2006. Her biochemical exams showed normal thyroid hormones (TSH: 0,27 mcg/mL - normal value 0,25-5,5; fT_3: 3,65 pg/mL - normal value 2,3-4,2; fT_4:1,03 pg/mL – normal value 0,75-1,8), negative thyroid antibodies and normal calcitonin (CT) (1 pg/mL, normal range 0-6 pg/mL) in June 2008. A scintigraphy with technetium, performed in 2005, revealed a large hypocaptant mass in the base of the left lobe and a small hypercaptant area in the isthmus (Figure **1**). Our thyroid ultrasound scan confirmed an hyperechoic nodule of 30x35x45 mm in the base of the left lobe, with intra and peripheral vascularization; other hypoechoic subcentrimetic nodules were evident in the right lobe and in the isthmus. No pathological lymph nodes were detected. Fine needle aspiration (FNA) biopsy of the left dominant nodule resulted Thy2, according to the Bethesda System for reporting thyroid cytopathology.

The patient underwent total thyroidectomy at the beginning of 2009. Gross examination showed a well defined left nodule of about 4 cm and an irregular whitish centimetric nodule in the isthmus (Figure **2**). The histology of the major nodule was compatible with benign adenoma, while the hypercaptant centimetric nodule of the isthmus appeared histologically composed of two distinct intermingled patterns (Figure **3**),

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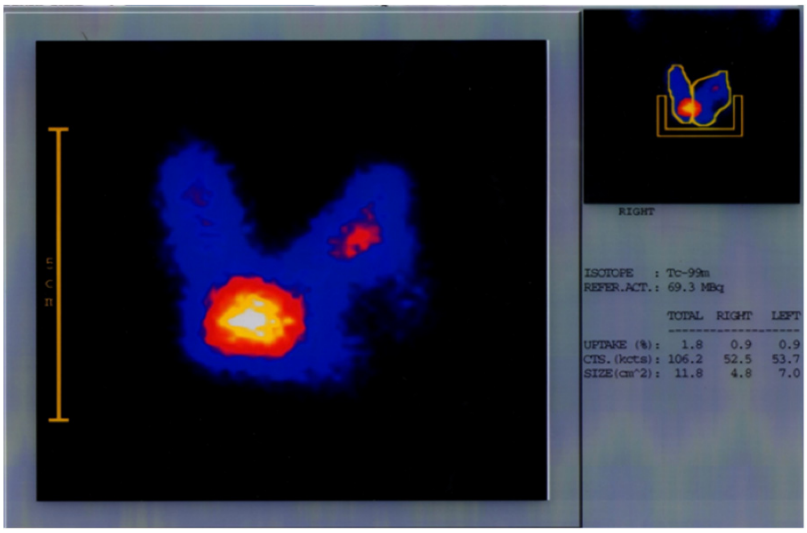

Figure 1: The scintigraphy with technetium shows a large cold area in the base of the left lobe and a small hot area in the isthmus.

Figure 2: On the left, nodule of about 4 cm in the base of the left lobe; on the right whitish centimetric nodule in the isthmus.

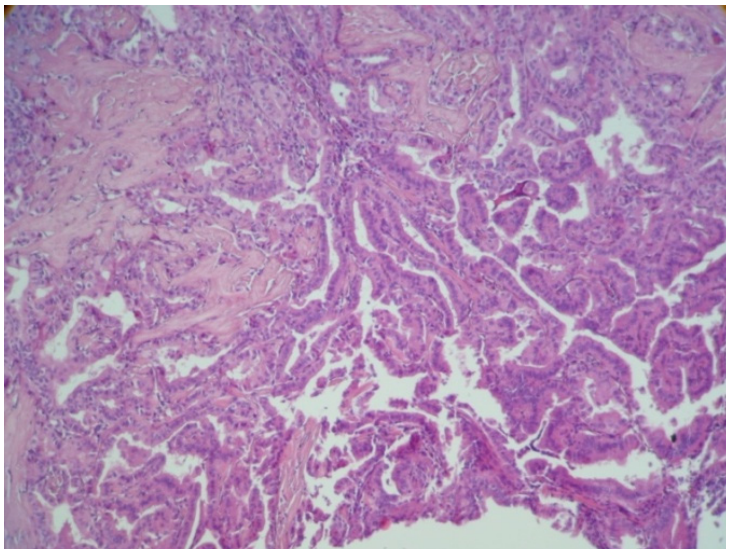

Figure 3: An overview of the papillary and medullary components of the MMPC.

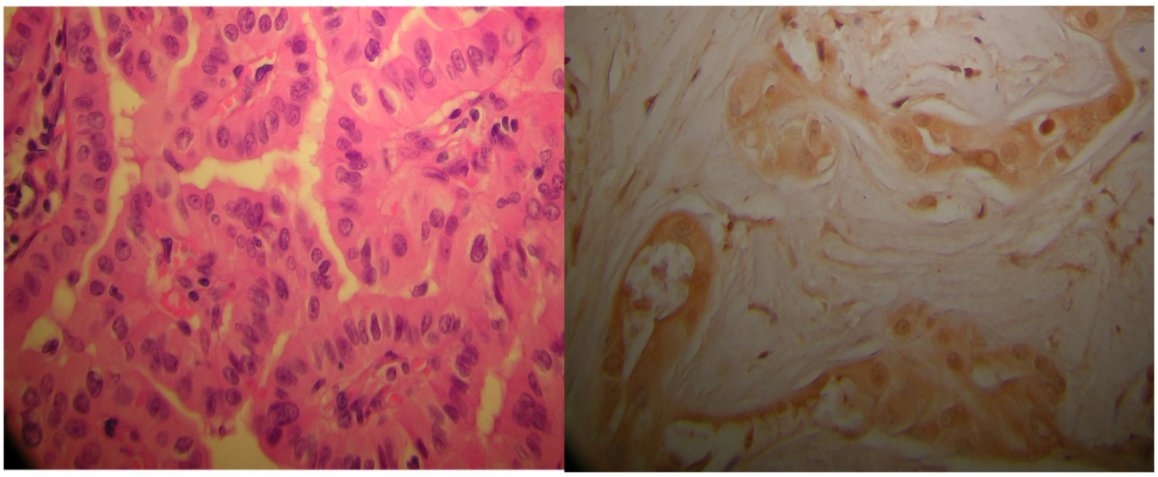

Figure 4: On the left, the papillary component with clear nuclei and occasional nuclear inclusions; on the right, the medullary component with positive immunostaining for calcitonin.

consistent with papillary and medullary carcinoma (Figure **4**).

At the immunohistochemistry, the PTC cells were positive for thyroglobulin and negative for calcitonin, while the MTC cells were strongly positive for calcitonin, CEA and Chromogranin A. Both the components were positive for TTF-1 and negative for synaptophysin. The final diagnosis was *mixed medullary papillary carcinoma* (pT1, pNx, pMx) in multinodular goiter. The patient started L-thyroixine (LT4) suppression therapy and underwent radioiodine ablation with 3112 mBq I^{131}. The whole-body scan with I^{131} performed six months after surgery was negative. Serum levels of thyroglobulin (TG), anti-thyroglobulin antibodies (TG-Ab), calcitonin were undetectable after surgery. These parameters were checked at the baseline and after stimulus test with thyrogen and pentagastrin/calcium gluconate every six months for the first two years and then annually with negative results. In conclusion, our patient appears clinically free of disease 5 years after surgery.

DISCUSSION

The simultaneous occurrence of MTC and PTC in the same thyroid is a rare phenomenon that can be observed as mixed tumor or collision tumor.

In the literature, there are several cases of collision tumor [4-19,36] and at least 13 cases of mixed medullary papillary carcinoma (MMPC) [19-28]. The clinical and histopathological features of MMPC cases are summarized in Table **1**. These tumors usually occur in the middle age as a swelling of the neck. The tumor size varies from 1 to 5 cm. The MMPC usually appears as unifocal lesion while multifocal tumors are associated with MEN 2 syndromes. Serum calcitonin is usually elevated.

The histogenesis of these tumors is still debatable. To date the most accepted hypothesis is the *hostage hypothesis,* proposed by Volante *et al*. [29]. According to the authors, the neoplastic parafollicular C cells entrap normal follicular cells and stimulate their proliferation. Subsequently, the hyperplastic and adenomatous follicles acquire a complete neoplastic phenotype.

Other hypotheses include the common stem cell origin of both neoplastic components and the divergent differentiation of MTC cells toward a follicular phenotype caused by molecular alterations [30].

Genetic analysis of RET oncogene in concurrent PTC and MTC has provided conflicting results [12,13,31-33]. In two cases [32,33], germline mutations of RET gene have been found in medullary and papillary cells, suggesting the potential role of these mutations in the development of both histological types. This hypothesis has not been confirmed by other cases of medullary papillary collision tumor, which have showed a different genetic origin of the two coexisting neoplasms. No somatic mutation of RET gene in both types of cells has been reported so far. Genetic alterations in the papillary carcinoma component of most mixed cases have not been studied or have not been found [31]. In few cases, MTC and PTC have been associated with somatic RET and BRAF mutations, respectively [13].

The histological appearance of MMPCs shows that the follicular structures are intimately admixed with the MTC, not only in the periphery of the nodule and they

Table 1: Mixed Medullary Papillary Carcinoma: A Review of the Literature

Author	Year	Sex	Age (yr)	pre-surgical CT (pg/mL)	FNA	Localization	Size (cm)	Lymph node metastases	Scinti-graphy
Albores-Saavedra *et al*. [20]	1990	M	29	n.a.	n.a.	Right lobe	6	Yes	Cold
Albores-Saavedra *et al*.	1990	M	36	n.a.	MTC	Left lobe	4	Yes	Cold
Lax *et al*. [21]	1994	F	49	indosable	PTC	Left lobe	-	-	Cold
Lax *et al*.	1994	F	49	indosable	-	-	-	-	Cold
Lax *et al*.	1994	M	28	n.a.	-	Right lobe	-	-	Cold
Apel *et al*. [22]	1994	M	48	-	-	Left lobe	-	Yes	-
Macak *et al*. [23]	1997	-	-	-	-	Left lobe	-	-	-
Shiroko *et al*. [24]	2001	F	77	1600	PTC	Right lobe	1,8	-	-
Dionigi *et al*. [19]	2007	M	65	294	n.a.	Isthmus	0,4	-	-
Nangue *et al*. [25]	2009	F	41	1140	MTC	Right lobe	3,2	-	n.a.
Hasney *et al*. [26]	2010	F	73	n.a.	n.a.	Left lobe	0,4	-	n.a.
Zoroquiain *et al*. [27]	2012	F	24	Normal	MTC	Right lobe	2	No	n.a.
Kataria *et al*. [28]	2013	M	35	-	-	-	-	Yes	-
Our case	2014	F	61	1	n.a.	Isthmus	1,2	No	Hot

CT: calcitonin, FNA: fine needle aspiration, MTC: medullary thyroid carcinoma, PTC: papillary thyroid carcinoma, n.a.: not available.

exhibit signs of cytological atypia and proliferation. These latter features are the clue to differentiate true mixed medullary papillary carcinomas from normal follicular structures entrapped in conventional MTCs. The neoplastic component of follicular derivation is composed of tumor cells displaying the typical architectural (papillary or follicular) and cytological features of PTC [14,34]. Some cases have been described within the multiple endocrine neoplasia 2a syndrome (MEN 2a) [29,35,36] while very few cases have been associated with the familial MTC (FMTC) [34,37].

In most cases, lymph node metastases have been found at the time of diagnosis, presenting as pure tumor cell populations of alternatively one or the other component or as an admixture of both components within the same tissue [22-24]. Distant metastases have been mainly described in the mediastinum, lung, liver, and bone [14,15,22,37,38]. Recently, a case of late medullary tumor recurrence in the upper mediastinum has been described in a patient misdiagnosed with papillary thyroid carcinoma14 years before [39].

The pre-surgical diagnosis of the mixed medullary papillary carcinoma is challenging. In fact, the role of FNA biopsy is limited and may lead to misdiagnosis. In presence of elevated serum calcitonin, immunohistochemistry for calcitonin and measurement of calcitonin in the wash-out fluid from fine needle aspiration increases the accuracy of the cytologic diagnosis of the medullary component. However, the definitive diagnosis of MMPC is based on immunohistochemical examination for calcitonin and thyroglobulin. The genetic screening is needed to exclude MEN 2 syndromes. Since the MMPC carries both medullary and papillary features, it requires specific treatment and follow-up. In particular, the treatment includes total thyroidectomy with central neck dissection, because of the medullary component and subsequent suppressive LT4 therapy and radioiodine ablation, because of the follicular component. The post-surgical follow-up includes neck ultrasound scan, periodic measurement of CT, basal and after stimulus test with calcium gluconate and mesurement of thyroglobulin and anti-thyroglobulin antibodies, basal and after stimulus test with thyrogen. The whole body scintigraphy and other imaging exams are reserved to patients with signs of recurrence or persistence of disease.

In our case, there were two confounding factors during the pre-surgical diagnosis: the normal serum calcitonin level and the hyperfunctioning thyroid nodule. Normal serum CT level has been already described in 3 cases of MMPC (Table **1**) and in 7 cases of pure MTC [27]. Malignancy has been rarely found in the

hyperfunctioning thyroid nodules, especially in adults, leading to difficulties in diagnosis. To the best of our knowledge, we described the first case of MMPC in a hot nodule at scintigraphy (Table **1**). Even if our patient underwent total thyroidectomy without central neck dissection, no signs of persistence or recurrence of disease have been found up to date. In our case, the genetic analysis on the nodule was not performed.

In conclusion, the appropriate immunohistochemical diagnosis of mixed medullary papillary thyroid carcinoma is mandatory for adequate treatment and follow-up. However, the prognosis is still unclear, because of the small amount of cases reported in literature.

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