Simultaneous occurrence of medullary and differentiated thyroid carcinomas. Report of 4 cases and brief review of the literature

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Abstract
Simultaneous occurence of medullary thyroid carcinoma (MTC) and papillary thyroid carcinoma (PTC) in a single patient is an unusual event. The incidence, cell origin, histopathology features and prognosis of these two carcinomas are considered completely different. *The aim of this retrospective study* was to describe clinical, pathologic characteristics and the prevalence of diagnosing such patients in our clinic. *Between October 2003 and December 2013, 1.420 consecutive patients* diagnosed by histology as having differentiated thyroid carcinoma (DTC) and treated with radioactive iodide (RAI) were retrospectively investigated. Of these, 4 patients were diagnosed by histology as having simultaneous MTC and PTC. The clinical and pathology characteristics of these patients are described. *The prevalence of simultaneous MTC and PTC* of these 4 patients in our clinic was 0.28% of all patients with DTC. The age of the 4 patients ranged from 44 to 63 years and were three females and one male. These patients are currently alive without disease from either of the two types of cancer. In two of these patients, MTC was located in the left and PTC in the right thyroid lobe. One patient had MTC in the right lobe and PTC in both lobes. The remaining patient had both cancers in the left lobe as a mixed tumor. We are able to present the pathology of only 2 of these 4 patients. In these 2 patients MTC was located in the left and PTC in the right thyroid lobe, one of them was female and the other was male, aged 44 and 49, respectively. *In conclusion*, our results suggested that simultaneous occurrence of MTC and PTC had a prevalence in our clinic of 0.28% among 1420 consecutive patients with DTC or 0.14%, if only the 2 patients in whom we are able to present their pathology slides are considered. Our cases suggest that these two tumors are usually independent and coincidental events in patients.

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Introduction

Simultaneous occurence of medullary thyroid carcinoma (MTC) and papillary thyroid carcinoma (PTC) in a single patient is a rare event. Information about these concurrent tumors is mainly based on case reports and recently on a few reviews [1-16]. Althought the true prevalence of these tumors is unknown, in a recent study their prevalence was reported to be 2.6% among patients with PTC [13]. These tumors have always been considered different from each other in terms of incidence, cell origin, histopathological features and prognosis [17-19].

Papillary thyroid carcinoma is the most common histologic type of thyroid carcinoma, accounting for 88% of all thyroid cancers in recent reports and originating from the follicular cells of the endoderm [17, 18]. This tumor is considered a relatively indolent tumor in which distant metastases and death are rare. Papillary thyroid carcinoma is a multicentric tumor in the thyroid gland excreting thyroglobulin (Tg) and thyroid hormones [18]. Follicular thyroid carcinoma (FTC) is the second most common thyroid malignancy, also arising from the follicular cells of the endodermy. Follicular thyroid carcinoma is often analyzed together with PTC, and both are known collectively as differentiated thyroid carcinoma (DTC) because of their similarities in clinical behavior, management, and outcome [20]. However, FTC is generally considered more aggressive with poorer prognosis compared with PTC and more likely to present with distant metastases on its initial diagnosis [20].

Medullary thyroid carcinoma derives from parafollicular C-cells of the ultimobranchial body of the neural crest and represents 5%-8% of all thyroid cancers [19]. Prognosis is generally worse than for PTC. Medullary thyroid carcinoma secrets calcitonin (CT) and other hormonal peptides and is considered part of the amine precursor uptake and decarboxylation system, of the thyroid. This carcinoma in the majority of cases (75%) is sporadic or may be part of various hereditary syndromes, like familial MTC or multiple endocrine neo-

plasia type 2 (MEN 2) [21-24]. Concurrent presence of MTC and PTC is limited [1-16].

The aim of this retrospective study was to describe the clinical and pathologic characteristics of 4 patients with simultaneous MTC and PTC in our Institution and specifically present the pathology slides that were available to us from only the 2 of these 4 patients.

Materıals and methods

Patients characteristics

Between October 2003 and December 2013 in our Institution, 1.420 consecutive patients were diagnosed by pathology as having DTC and were treated by total thyroidectomy and ablation of the remnant with radioactive iodide (RAI). Of these, 4 patients had simultaneous MTC and PTC, 3 with follicular variant (Table 1). We are unable to present the histopathology slides of 2 of these 4 patients who referred to us from another hospital. The histopathology slides available to us were reexamined according to the diagnostic WHO standards for MTC, PTC and FTC (Fig. 1-5). Clinical, pathologic characteristics and the follow-up of all 4 patients are described in Table 1. The protocol of this study was approved by our Local Ethics Committee.

All patients are currently alive and well. According to our protocol, all cases before treatment underwent neck ultrasonography, chest radiography and/or thorax unenhanced computed tomography for the presence of residual thyroid tissue, lymph node involvement, or distant metastases. Treatment with 3.7GBq of RAI for the ablation of residual thyroid tissue or with 5.5-7.4GBq in cases of extrathyroidal invasion, lymph node or distant metastases was carried out. A post-treatment scan was obtained 7-12 days after RAI treatment, and patients were discharged in about 2 or 3 days after the emitted radiation level was <40μSv/h, measured at 1m from the patient.

Six to nine months after RAI ablation, the patients underwent whole body scan to confirm the success of ablation. All patients received suppressive doses of thyroxine (T4) to maintain serum thyroid-stimulating hormone (TSH) concentration suppressed to undetectable levels (<0.15mIU/L) and were followed-up at intervals of 6-12 months. Patients were monitored annually as outpatients in accordance with a standardized follow-up protocol that included clinical examination, neck ultrasonography, Tg levels and were attented by an endocrinologist who ordered more tests when necessary.

Results

None of our patients had a family history of thyroid carcinoma, pheochromocytoma, primary hyperparathyroidism or radiation exposure. The clinical characteristics of all patients and their final diagnosis are presented in Table 1. Patients numbered 1 and 2 had their histology slides reexamined and are presented in Figures 1-5. According to the preoperative diagnosis, 3/4 patients had a proliferative lesion suspicious for malignancy. The remaining 1 patient had elevated serum CT, and histopathological diagnosis positive for MTC (Table 1, case 2).

Table 1. *The clinical and histopathological characteristics of all four patients with simultaneous occurrence of medullary and papillary thyroid carcinomas some with follicular variant. Cases 1 and 2 had their histopathology slides reexamined by us.*

Case No	Age years/ Gender	FNA	Histopathology	Size (cm) / Side	RAI treatment GBq	Follow-up (y)
1	49 / M	Suspicious	mMTC PTC	0.2 / L 5.5 / R	5.5	2
2	44 / F	MTC	MTC mPTC (FV)	1 / L 0.5 / R	3.7	8 8
3	63 / F	Suspicious	MTC PTC (FV)	2.5 / R 0.6-0.4 / R 4.0-1.0 / L	6.5	3
4	56 / F	Suspicious	MTC+PTC (FV)*	4.9 / L	3.7	6

*MTC: medullary thyroid carcinoma; PTC: papillary thyroid carcinoma; mPTC: papillary thyroid microcarcinoma; mMTC: medullary thyroid microcarcinoma; F: female; M: male, R: right; L: left; FV: follicular variant; FNA: fine needle aspiration. *Mixed tumor MTC and PTC*

Table 2. *Preoperative biochemical findings*

Case No	CEA (0-4ng/mL)	CT (0-30pg/mL)	Tg (0.3-4.94ng/mL)
1	N	N	N
2	N	690	N
3	N	N	109.6
4	343.1	N	N

CEA: carcinoembryonic antigen; CT: calcitonin; Tg: thyroglobulins; N: normal

Preoperatively triiodothyronine (T3), T4, TSH, serum calcium and parathormone were within normal limits in all patients. Baseline serum CT in case 2, Tg in case 3 and carcinoembryonic antigen (CEA) in case 4 measured by chemiluminescent microparticle immunoassay (CMIA) were high (Table 2). Serum CT in case 2 decreased to normal at 1 month after thyroidectomy. Serum Tg level in case 3 decreased to normal at 2 months after RAI treatment and CEA in case 4 decreased to normal at 4 months after thyroidectomy.

All our patients underwent bilateral total thyroidectomy. One patient had prophylactic lymph nodes dissection due to the preoperative diagnosis of MTC. (Table 1, case 2). None of the 4 patients had metastatic lymph nodes or distant metastases at the time of initial presentation.

Using immunohistochemistry, strong immunoreactivity for CT, for chromogranin A and for CEA was found in case 1 patient (Fig. 3). Amyloid deposits were present in cases 1 and 2 (Table 1).

Postoperative RAI treatment and TSH suppressive treatment were performed in all patients. During the follow-up period, serum levels of Tg, anti-Tg Ab, and CT were routinely checked.

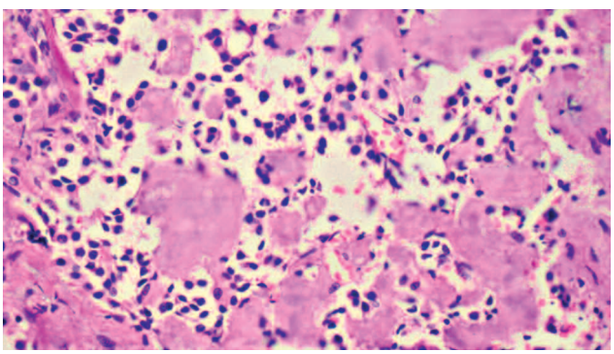

Figure 1. Case 1: Medullary microcarcinoma comprised of cells with eccentrically located round nuclei with "salt and pepper" chromatin and with amyloid aggregates (hematoxylin and eosin stain, original magnification x400).

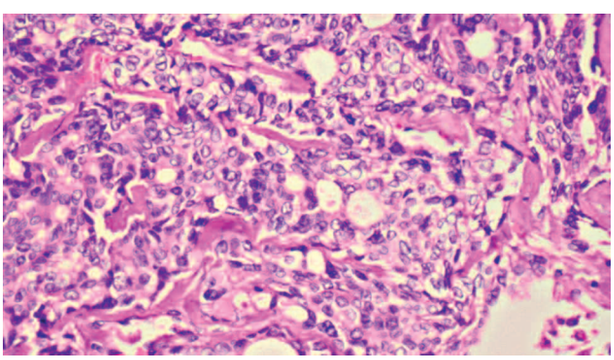

Figure 2. Case 1: Photomicrograph shows the papillary carcinoma located in the right lobe of the thyroid (hematoxylin and eosin stain, original magnification x400).

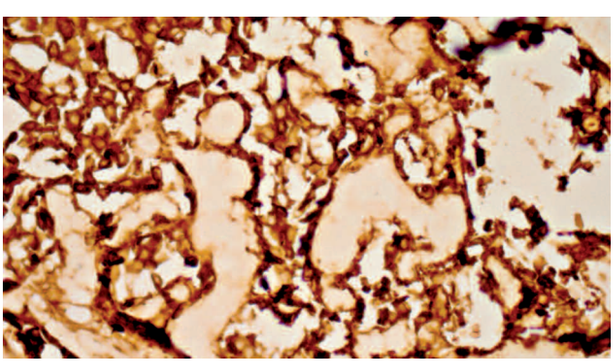

Figure 3. Case 1: Immunhistochemical carcinoembryogenic antigen positivity in medullary carcinoma, original magnification x400.

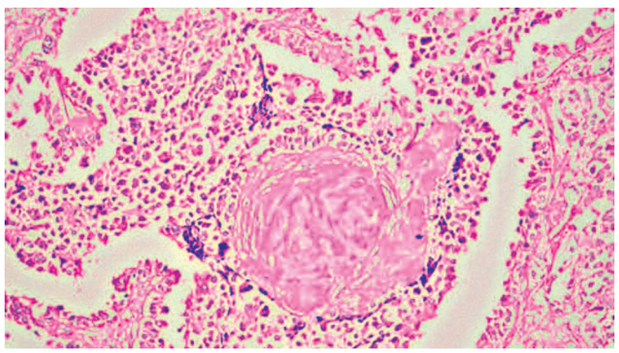

Figure 4. Case 2: Photomicrograph reveals MTC comprised of cells with eccentrically located nuclei. The pink, homogenous amyloid material is in the center. (hematoxylin and eosin stain, original magnification x200).

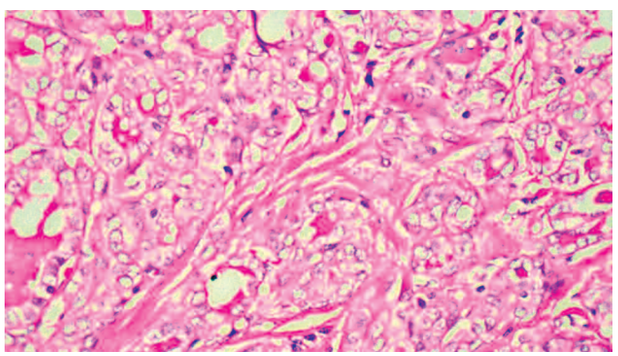

Figure 5. Case 2: Papillary carcinoma showing follicules with nuclear crowding, vesiculation and nuclear grooves. Note the scant but dense colloid found in the follicle lumens (hematoxylin and eosin stain, original magnification x400).

Discussion

The simultaneous occurrence of MTC and DTC in the same thyroid gland can be observed in two main settings: a mixed tumor showing dual differentiation or a collision tumor showing two separate different carcinomas. Our cases numbered 1 and 2 had both carcinomas in different thyroid lobes MTC was located in the left and DTC in the right thyroid lobe. In case number 3, MTC was located in the right and DTC in both thyroid lobes as multifocal. In the present study, there was no apparent side predominance of MTC and DTC. Reviewing the literature, most cases of concurrent MTC and DTC were found to have no apparent side predominance, as our cases [1-9].

Mixed medullary-papillary carcinoma of the same thyroid in a single nodule as in our case number 4 is extremely rare [1-6, 23]. Wong et al. (2012) [10] described 84 patients with mixed MTC/DTC among 75.449 patients with DTC alone. This is a prevalence of 0.11%. Our all cases had separate PTC components. Albores-Saavedra et al. (1990) first reported two cases of mixed MTC and PTC in one tumor with the papillary component presenting a follicular variant, as our 3/4 cases [1].

The presence of MTC with simultaneous PTC in two separate foci was initially reported by Lamberg et al. in 1981 [7]. Other researchers reported high rates of separated PTC in patients with MTC ranging from 14% to 19% and a high prevalence (78% and 90%, respectively) of mPTC [8, 9]. None of these patients had a FTC component. Kim et al. (2010) con-

cluded that simultaneous MTC/PTC simply represented a primary MTC with an incidental mPTC [9] and hypothesized that this could be the result of both an increasing incidence and a more efficient pathological diagnosis of PTC and more specifically of mPTC during the last decade. Machens et al. (2012) [13] reported that the rate of MTC in separate foci among patients with PTC was 2.6%. Wong et al. [10] described 162 patients in the form of mixed or of two separate tumors among 75.449 patients with DTC alone (a prevalence of 0.21%). In our study, 0.28% of patients with DTC displayed simultaneous MTC. Other researchers reported higher prevalence of these two tumors in DTC patients [8, 9, 13], which could be due to different selection of patients. Other researchers reported that one of these tumors is primarily detected and the other detected incidentally after thyroidectomy [10].

Most cases of concurrent MTC and PTC in the literature have been coincidentally identified [8-14] as were our cases.

The majority of mixed or concurrent MTC/DTC occur in a sporadic form and rarely in hereditary syndromes as MEN type 2 or familial non-MEN MTC [19]. There are limited case reports in the literature describing mixed or independent tumors in separate foci of simultaneous MTC/DTC associated with hereditary syndromes [21-24]. However, in our patients, a negative family history and late onset of the symptoms suggested the presence of sporadic MTC/PTC.

The exact pathogenesis of these tumors is still controversial. Theories describe a common stem cell or the same neoplastic stimuli resulting in the simultaneous transformation of C and of the follicular cells or suggest a common mutation rearranged during transfection (RET) and after MTC trapping of normal follicle cells [9-27]. Alternatively, the collision theory suggests that MTC and DTC are two independent tumors located in the same thyroid by coincidence [3, 8, 9, 27, 28]. The observation that our 3/4 cases showed the MTC and the PTC in contralateral lobes strongly supports the theory of independent events. Two independent thyroid carcinomas in the same patient have also been described and were considered as simple coincidence. As for carcinomas it is very seldom, indeed, that three different carcinomas be described in the same patient [29]. Although the causative factors for multiple primer carcinomas are not known, factors like family history, genetic and immunologic factors may support carcinogenesis [29].

Compared with MTC alone, it has been suggested [8, 10] that patients with simultaneous MTC/DTC did not differ in the epidemiologic, clinical, or pathologic features.

In conclusion, we described four rare cases of concurrent occurrence of MTC and DTC treated with total thyroidectomy and RAI ablation of the remnant in our institution, of which we present the histology of the two of them. Simultaneous occurrence of MTC and PTC (3/4 with a follicular variant) in our patients showed a prevalence of 0.28% among 1420 consecutive patients with DTC or 0.14%, if only the 2 patients in whom we are able to present their pathology slides are considered. Our cases support the theory that these two tumors are usually independent and represent a coincidental event. Additional studies are necessary to clarify any potential biologic relationship between simultaneous MTC and PTC.

The authors declare that they have no conflicts of interest.

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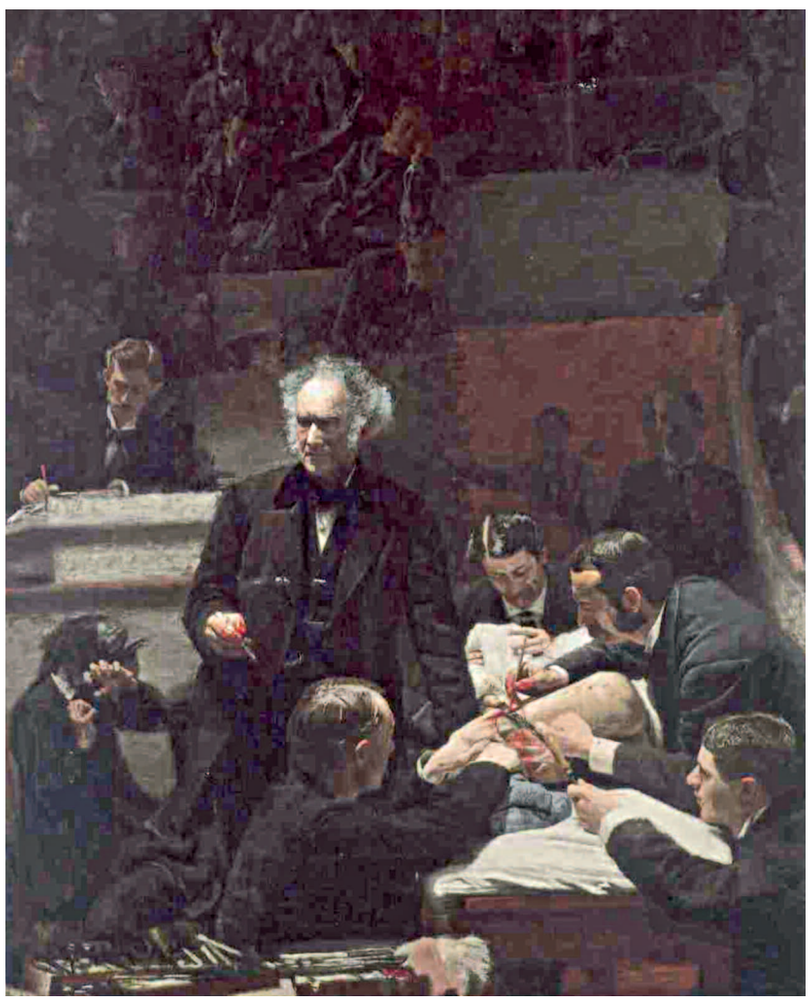

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