CASE REPORT

ISSN 1598-1703 (Print)
ISSN 2287-6782 (Online)
Korean J Endocr Surg 2014;14:167-170

The Korean Journal of
Endocrine Surgery

Synchronous Occurrence of Papillary, Follicular, and Medullary Carcinoma in the Same Thyroid Gland

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Incidence of thyroid carcinoma has increased dramatically; however, simultaneous occurrence of different tumors in a single thyroid gland is rare and the embryologic or molecular explanations for such cases lack a solid basis. We report on a 67-year-old woman who underwent surgery for cytologically undetermined nodules in the bilateral thyroid glands. Postoperative pathology findings indicated synchronous occurrence of discrete papillary, follicular, and medullary thyroid carcinoma. She has remained disease-free after postoperative radioactive iodine therapy (130 mCi). This is the fifth report on the synchronous occurrence of different tumors in a single thyroid gland worldwide, and the first ever in Asia.

Key Words: Papillary thyroid carcinoma, Follicular thyroid carcinoma, Medullary thyroid carcinoma, Synchronous neoplasms

Received July 15, 2014,
Revised September 2, 2014,
Accepted September 3, 2014
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INTRODUCTION

Differentiated thyroid carcinoma is categorized into 3 groups: papillary, follicular, and medullary thyroid carcinoma.(*1*) Papillary and follicular thyroid carcinomas arise in follicular cells, which originate from the foregut endoderm, whereas medullary thyroid carcinomas develop in parafollicular C-cells, which are derived from the neuroectoderm. Each neoplasm shows different characteristics on histology, displays distinct biologic behaviors, and is associated with different prognoses.(*2-4*)

Multifocal growth of thyroid tumors is frequently identified, especially in papillary thyroid carcinomas.(*5*) However, synchronous occurrence of different carcinomas in a single thyroid gland is rare.(*6-12*) Here, we report on an extremely rare case of synchronous papillary, follicular, and medullary thyroid carcinoma, and perform a review of the literature.

CASE REPORT

A 67-year-old woman presented at our hospital with a chief complaint of a palpable mass on her anterior neck. Her family history was free of any endocrine or non-endocrine malignant tumors, and she had no previous history of specific medication or surgery.

On physical examination, a mass, approximately 4 cm in size was palpated on her right anterior neck. Neck ultrasonography revealed a 4.4 cm heterogeneous iso-echoic nodule in the right thyroid and a 1.2 cm low-echoic nodule in the left thyroid. There was no cervical lymph node enlargement (Fig. 1). The thyroid function was normal, with mild elevation of thyroglobulin Ag (43.3 ng/μL;

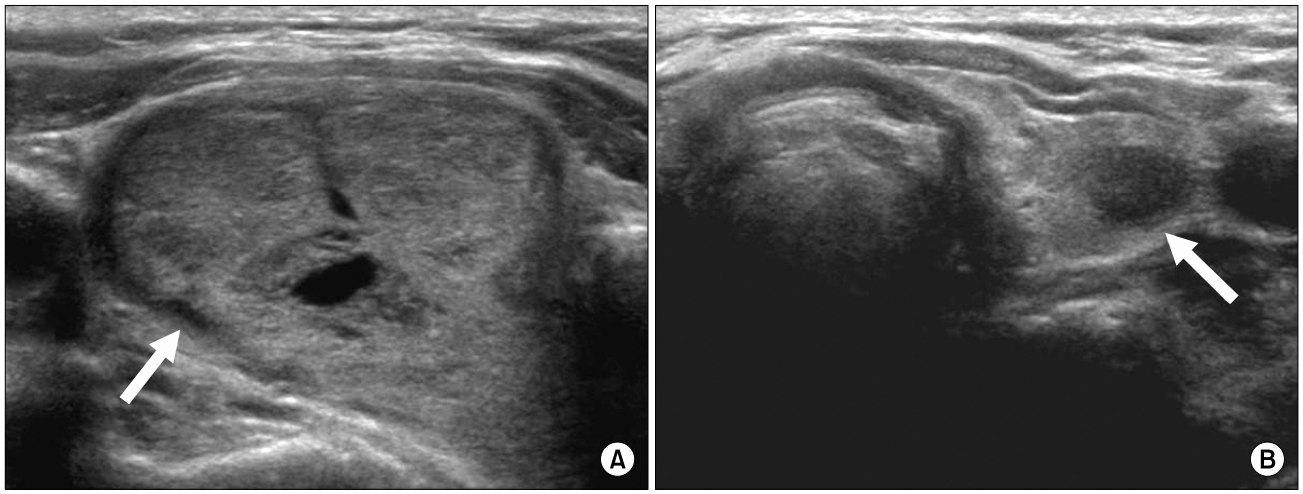

Fig. 1. Ultrasonographic features of the bilateral thyroid nodules, axial view. (A) A 4.4 cm heterogeneous iso-echoic nodule on the right lobe and (B) a 1.2 cm low-echoic nodule on the left lobe (arrows) were noted.

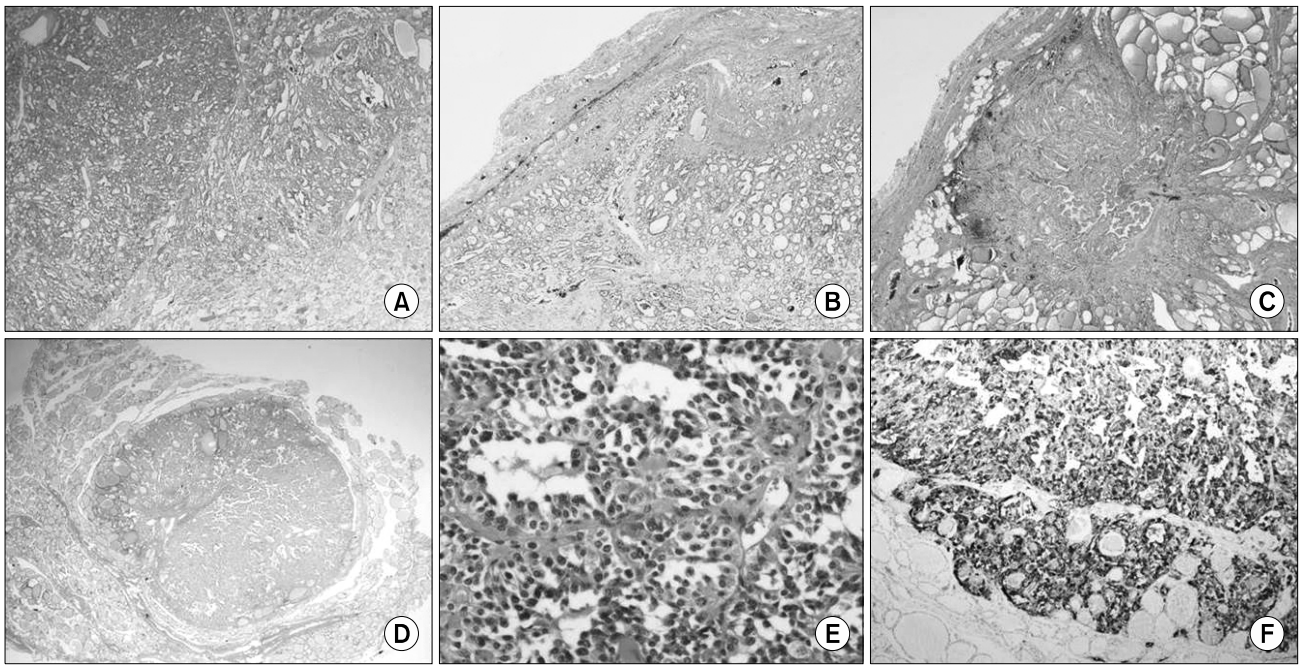

Fig. 2. Microscopic features of the follicular, papillary, and medullary thyroid microcarcinomas in bilateral lobe. (A, B) Follicular thyroid carcinoma in the right lobe. Infiltrative growth of tumor cells beyond the capsule was identified (hematoxylin and eosin [H & E] stain, ×40). (C) Papillary thyroid microcarcinoma. Typical papillary histologic features were seen (H & E stain, ×40). (D, E) Infiltration of tumor cells with small round nuclei was identified in medullary thyroid carcinoma of the left lobe (hematoxylin and eosin stain, ×40, ×200). (F) Strong positivity of medullary thyroid carcinoma was noted upon calcitonin immunostaining (×100).

normal range, 0.1~32.5 ng/μL). The serum calcitonin level was not investigated.

The patient underwent fine-needle aspiration biopsy (FNAB) of the bilateral nodules. The cytology results revealed atypia of follicular cells with undetermined significance for the left thyroid mass, and a benign follicular nodule for the right mass.

Although the cytology results did not reveal any malignant nodules, we recommended thyroid resection because of the large size and low-suspicious features of the nodules. However, the patient was reluctant to operation, and preferred receiving routine check-ups with ultrasonography and FNAB.

For 2 years after the initial presentation, there were no

definite changes in the ultrasonographic features of the bilateral nodules. However, the sizes of the bilateral thyroid masses were slightly increased (approximately 0.1～0.2 cm). After the 2-year check-up, the patient agreed to undergo operation.

We performed bilateral total thyroidectomy and central neck dissection. On review of the surgical specimen, surprisingly, 3 kinds of thyroid carcinomas (papillary, follicular, and medullary thyroid carcinoma) were concurrently identified in the bilateral lobes. The hypoechoic nodule on the left lobe was diagnosed as a medullary thyroid carcinoma, 0.8 cm in size, whereas the heterogeneous nodule on the right lobe was determined to be 4.3 cm-sized follicular thyroid carcinoma with capsular invasion. Additionally, a 0.3 cm-sized isolated papillary thyroid microcarcinoma, which was not identified in the preoperative ultrasound, was observed in the upper pole of the right lobe. No metastasis was found in 3 adjacent resected lymph nodes (Fig. 2).

The postoperative serum calcitonin was normal, and sequence analysis of the RET proto-oncogene from peripheral blood leukocytes showed no mutations in exons 10, 11, 13, 14, 15, and 16. The patient was discharged 3 days after operation. She received postoperative radioactive iodine therapy of 130 mCi, and was disease-free at the latest follow-up (7 months post-surgery).

DISCUSSION

Although the incidence of thyroid carcinoma is dramatically increasing in recent years, simultaneous occurrence of different tumors in a single thyroid gland is still a rare event. Since Lamberg et al. first reported on the coexistence of papillary and medullary thyroid carcinomas, approximately 70 cases of synchronous presence of 2 types of thyroid carcinoma have been reported.(*6,11*) In contrast to these cases, thyroid tumors containing mixed histologic features (medullary-papillary or medullary-follicular) within a single lesion are relatively frequently identified.(*12*)

Conversely, the simultaneous occurrence of 3 types of carcinomas is extremely rare. To our knowledge, only 4 previous cases have been reported in the literature to date (Table 1). Including the present case, there were 2 and 3 cases involving men and women, respectively, and none of the cases had a family history of endocrine disease or previous exposure to irradiation. Genetic analyses for RET proto-oncogene mutations were performed in 2 of the previously reported cases, and, similarly to in our case, no variations were identified. Four cases, including ours, maintained a disease-free status during the follow-up periods, whereas 1 patient experienced multiple metastases of follicular thyroid carcinoma to the liver and lung.

Several theories have been formulated to explain the coexistences of different tumors, including the 'common stem cell theory', which is based on the presence of common progenitor cells of follicular and parafollicular C-cells. According to this theory, common stem cells undergo neoplastic transformation first and are differentiated into the 2 different subtypes of cells thereafter.(*13,14*) Another potential hypothesis is the 'field effect theory', which suggests that a common oncogenic stimulus leads to a synchronous transformation of both follicular and parafollicular C-cell progenitor cells.(*15*) However, many clinicians regard this coexistence of multiple tumors as a mere coincidence.

Recent molecular studies have revealed several gene mutations related to thyroid carcinoma.(*6,13,16*) Until recently, the RET proto-oncogene received most attention,

Table 1. Previous reports of cases of synchronous papillary, follicular, and medullary thyroid carcinomas

No.	Year of report	Sex/age (years)	Family/personal history	Molecular studies	Prognosis
1	1992	F/27	None	Not performed	NED for 2 years
2	1999	F/33	None	Not performed	Not documented
3	2005	M/52	Previous transient sepsis (+)	RET germline mutation (−)	Multiple liver and lung metastases
4	2013	M/64	None	RET germline mutation (−)	NED for 2 years
5*	2014	F/67	None	RET germline mutation (−)	NED for 7 months

NED = no evidence of disease. *Present study.

as it appears to be related with both follicular and parafollicular C-cell originated tumors. Germline missense mutations of the RET proto-oncogene are commonly identified in familial medullary thyroid carcinomas and are also found in 30~50% of sporadic cases.(*13,16*) Furthermore, point mutations and rearrangement of RET can give rise to the chimeric oncogene RET/PTC, which correlates with the occurrence of papillary thyroid carcinoma.(*16*) Although these variations are discrete events, the potentiality of the RET proto-oncogene as the common cause of multiple neoplasms has been getting consistent attention. In our case, as well as in the 2 previous reports, only the germline mutations of RET were investigated, and no case showed genetic variations.

The embryologic or molecular explanations for the synchronous occurrence of different thyroid carcinomas still lack a solid basis, and the most likely explanation may simply be that it is a mere coincidence. Careful and meticulous examinations of surgical specimens are important to not miss these synchronous tumors. We will carefully follow-up our patient, and will continue to identify and examine similar cases.

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