

# A Case of Concurrent Papillary and Medullary Thyroid Carcinomas Detected as Recurrent Medullary Carcinoma after Initial Surgery for Papillary Carcinoma

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As the prevalence of thyroid carcinoma is rapidly increasing, coexisting subtypes of thyroid carcinomas are often found. However, concurrent papillary and medullary carcinomas in the thyroid gland are extremely rare. We report the case of a 50-year-old man with co-occurrence of multiple papillary and medullary thyroid carcinomas; the latter were undetected at initial diagnosis. Sixty-three months after the initial operation performed because of papillary carcinoma diagnosis, a metastatic lymph node was detected in the left level IV region, which was revealed as medullary carcinoma. The histopathologic results from initial surgery were reviewed, and we found multiple coexisting medullary carcinomas that were not identified initially. The incidence of concurrent papillary and medullary thyroid carcinomas will continue to increase as rates of diagnosis of and surgery for thyroid carcinoma increase. Therefore, surgeons and pathologists should be aware of the possible coexistence of subtypes of thyroid carcinomas to avoid missing concurrent lesions.

**Key Words:** Thyroid cancer, Papillary carcinoma, Medullary carcinoma

## Introduction

With the rapid increase in thyroid carcinoma prevalence, thyroid carcinoma subtypes are often coexist. Most of these cases are of co-occurrences of papillary and follicular thyroid carcinomas, originating from the same embryonic follicular thyroid cells. However, a possible relationship between papillary carcinoma and medullary carcinoma, despite their distinct origins, has been suggested.<sup>1)</sup> Furthermore, a recent German study has reported an increase in the incidence of concurrent papillary and medullary carcinomas.<sup>2)</sup>

However, given that 80–90% of thyroid carcinomas are still of the papillary subtype and concurrent papillary and medullary carcinoma in the thyroid gland is very rare, definitive papillary carcinoma features on histopathological examination might cause pathologists to ignore possible concurrent medullary carcinomas. This is, particularly likely when the medullary carcinoma is small and its tumor markers, such as calcitonin and carcinoembryonic antigen (CEA), are not evaluated.<sup>3)</sup> We encountered a case of a 50-year-old man with concurrent papillary and medullary carcinomas; the medullary carcinomas were undetected at the initial diagnosis. We detected the medullary carcinomas

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coexisting with the initial papillary carcinomas after medullary carcinoma recurrence at regional lymph nodes.

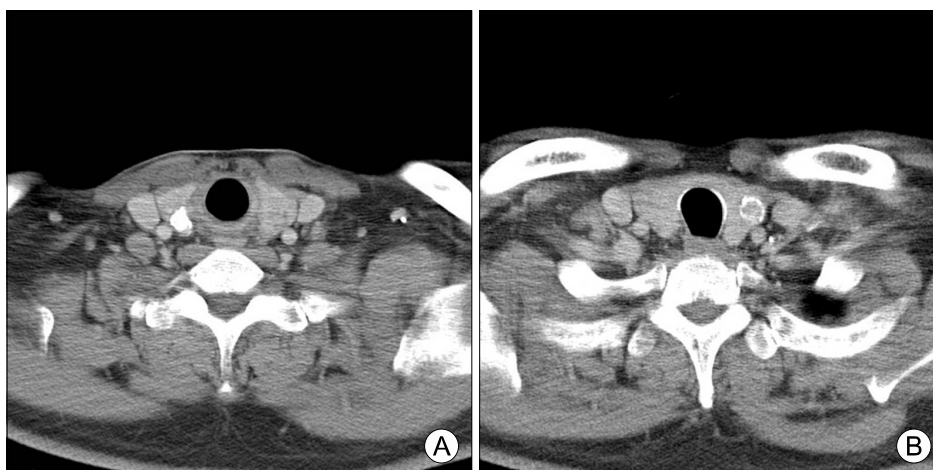
## Case Report

A 50-year-old man was referred to our department with an incidental finding of thyroid nodules, with severe calcification on ultrasonography (US). Aspiration cytology indicated papillary thyroid carcinoma in both calcified nodules.

The 2 thyroid nodules were easily palpable during physical examination at the right and left thyroid lobes. The patient had no specific symptoms for these nodules, and no personal/family history of endocrine disorders or previous external radiation therapy. Serum levels of calcium, thyroid-stimulating hormone, and free thyroxine were within the normal ranges, whereas anti-microsomal and anti-thyroglobulin auto-antibodies were elevated, at >3000.0 U/mL (normal range, 0–60 U/mL) and 130.1 U/mL (normal range, 0–35 U/mL), respectively. However, the patient had no history of chronic thyroiditis. Serum calcitonin levels were not evaluated because guidelines issued by several thyroid organizations did not recommend routine calcitonin examination for evaluating thyroid nodules due to cost-effectiveness and uncertain clinical significance.<sup>4)</sup> Cervical contrast-enhanced computerized tomography (CT), with a 3.5-mm slice thickness, indicated a 1.4-cm calcified nodule at the mid-posterior portion of the right thyroid gland and a

1.5-cm nodule with egg-shell calcification at the low-lateral portion of the left thyroid gland (Fig. 1). US and CT did not show evidence of lymph node metastasis in the central and lateral compartments of the neck. On the basis of these evaluations, multiple papillary carcinomas were diagnosed, and we conducted total thyroidectomy with bilateral central neck dissection. Histopathological results indicated a 1.5-cm conventional papillary carcinoma with an extra-thyroidal extension in the right thyroid gland and a 0.8-cm conventional papillary carcinoma within the left thyroid gland. From 3 nodes in the left central compartment, 1 metastatic papillary carcinoma was identified, with no metastatic lymph node on the right side. The patient underwent radioactive iodine remnant ablation using 150 mCi <sup>131</sup>I and was monitored regularly.

Sixty-three months after the initial operation, a suspicious lymph node with hyperechogenicity was detected on the posterolateral aspect of the “internal jugular vein” in the left level IV region on US. Contrast-enhanced neck CT also showed a suspicious lymph node with obvious enhancement at the same region (Fig. 2). Aspiration cytology on this lymph node revealed metastatic medullary carcinoma rather than papillary carcinoma. Following this diagnosis, histopathologic results from the previous surgery were carefully reviewed, and paraffin-embedded specimens were re-cut by another pathologist specializing in thyroid pathology. Hematoxylin and eosin staining showed a suspicious area of amyloid

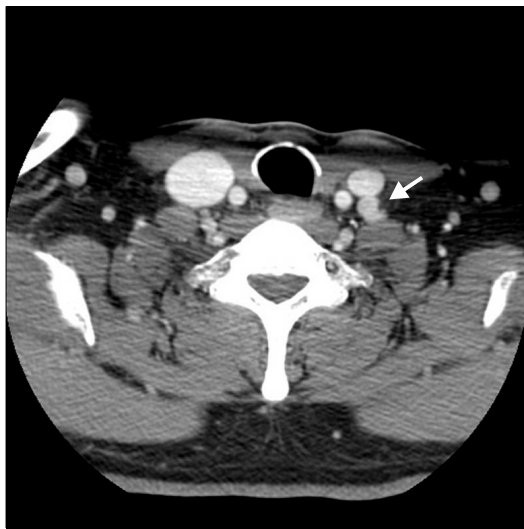


**Fig. 1.** Initial cervical CT scan shows a 1.4-cm calcified nodule at the mid-posterior portion of the right thyroid gland (A) and a 1.5-cm nodule with egg-shell calcification at the low-lateral portion of the left thyroid gland (B).

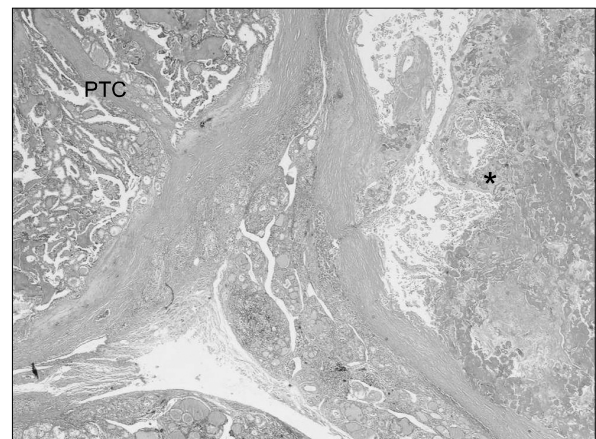
deposition that had been regarded as fibrosis or a hyalinized stroma portion adjacent to the papillary carcinoma nodule in the left thyroid lobe (Fig. 3). Using several immunohistochemical stains, we eventually identified 2 lesions that had strikingly different morphologies but were close to each other. One nodule of 0.8 cm diameter, which had been diagnosed as papillary carcinoma, was negative for calcitonin, CEA, and synaptophysin. In contrast, another nodule adjacent to the papillary carcinoma had a diameter of

0.9 cm; was focally immunoreactive for calcitonin, CEA, and synaptophysin (Fig. 4); and was diagnosed as medullary carcinoma (Fig. 5). The medullary carcinoma was lateral to and less than 1 mm away from the coexisting papillary carcinoma in the left thyroid gland, but each nodule had its own capsule. Interestingly, several 1–2 mm medullary carcinoma lesions were scattered in the right thyroid gland.

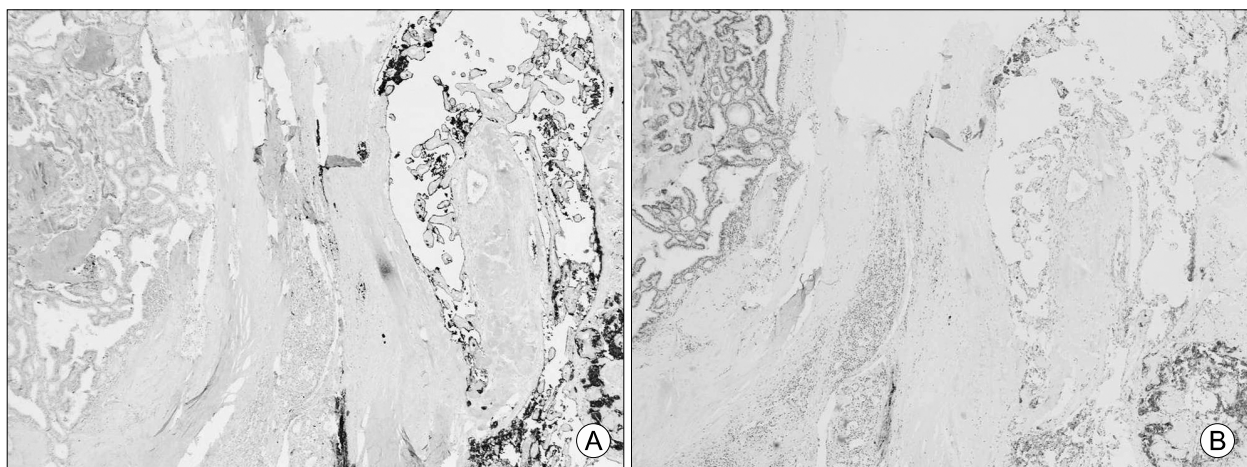
Preoperative calcitonin levels at the time of the second surgery were significantly elevated, at 157.0 pg/mL (normal range, <10 pg/mL). The patient underwent selective neck dissection from levels II to V, and 5 of 23 lymph nodes at level III and IV showed



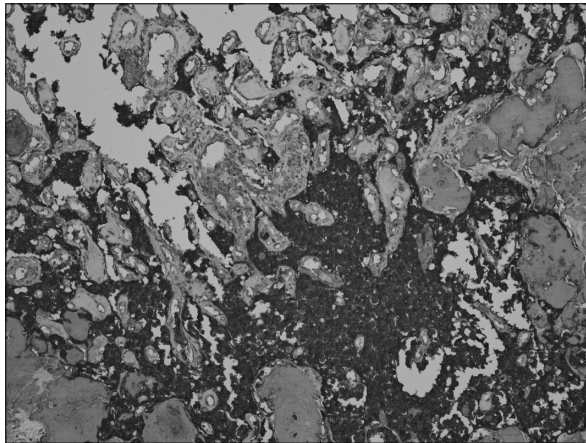
**Fig. 2.** Follow-up CT scan indicates a metastatic lymph node (arrow) with obvious enhancement on the posterolateral aspect of the “internal jugular vein” in the left level IV region. Aspiration cytology of this lymph node revealed metastatic medullary thyroid carcinoma.



**Fig. 3.** A suspicious medullary carcinoma nodule (asterisk) was identified just adjacent to a known papillary carcinoma nodule on the re-cut slide. The 2 nodules were separated from each other by their own capsules (Hematoxylin & eosin stain,  $\times 20$ ).



**Fig. 4.** Carcinoembryonic antigen (A) and synaptophysin (B) staining indicate positive reactivity on the left nodule (medullary carcinoma) and negative reactivity on the right nodule (papillary carcinoma) (carcinoembryonic antigen and synaptophysin,  $\times 200$ ).



**Fig. 5.** Tumor cells in medullary carcinoma reveal diffuse strong cytoplasmic positive reactivity on calcitonin immunohistochemical staining (calcitonin,  $\times 100$ ).

evidence of metastatic medullary carcinoma. RET proto-oncogene analysis revealed negative result for mutation and BRAF mutation was not found at codon 600. His calcitonin level had decreased to the normal range at 8.8 pg/mL on the third postoperative day and to 0.1 pg/mL in a month after operation.

The patient is healthy, with no evidence of recurrence, 35 months after the second surgery.

## Discussion

Medullary carcinoma is a rare and aggressive type of thyroid carcinoma with several distinctive features that distinguish its management from that of well-differentiated thyroid carcinomas. However, the histopathological features of medullary carcinoma cells are often similar to those of other tumor cells such as acinar, follicular, papillary, small, giant, clear, and oxyphilic cells, and even simple hyalinized stroma as in this case.<sup>5,6)</sup> Therefore, confirmation of medullary carcinoma mainly depends on immunohistochemical staining rather than examination of Hematoxylin and eosin stains.<sup>5)</sup> In this case, we initially missed the coexisting medullary carcinoma even though it was multiple and very close to a typical papillary carcinoma nodule. Guidelines issued by several organizations including the American Thyroid Association (ATA) and National Comprehensive Cancer Network (NCCN) do not recommend either for or against for the routine

measurement of serum calcitonin for evaluating thyroid nodules.<sup>4,7)</sup> We did not measure serum calcitonin during the initial diagnostic evaluation, and aspiration cytology on both nodules indicated papillary carcinoma. We assume that these circumstances and the rarity of co-occurring papillary and medullary carcinomas led us to ignore other possible explanations. However, the surgical extent would have not changed because we initially conducted total thyroidectomy with bilateral central neck dissection. We are now of opinion that routine serum calcitonin measurement during the initial diagnostic evaluation of thyroid nodules facilitates unsuspected medullary thyroid carcinoma detection.<sup>7,8)</sup>

Co-occurrence of papillary and medullary carcinomas was initially described by Lamberg et al.<sup>9)</sup> in 1981. In 1989, the World Health Organization (WHO) classification system defined mixed medullary and follicular thyroid carcinoma (MMFTC) as a tumor showing both the morphological features of medullary carcinoma together with calcitonin immunoreactivity, and the morphological features of carcinoma originating from follicular cells, including papillary carcinoma and follicular carcinoma, together with thyroglobulin immunoreactivity.<sup>10)</sup> According to the study reported in 2010, 65 cases of co-occurrence of papillary and medullary carcinomas were recorded in the literature.<sup>1)</sup> However, only 7 cases had multiple medullary carcinomas.<sup>1)</sup> Most reported cases displayed well-separated papillary and medullary components, indicating simple concurrent medullary carcinoma with papillary carcinoma, not an MMFTC as classified by WHO.

Various hypotheses have been postulated to explain the co-occurrence of papillary and medullary carcinomas. The first is the common stem cell theory suggesting that the ultimobranchial body has uncommitted stem cells that can differentiate into both follicular and parafollicular cells.<sup>11)</sup> However, molecular evidence suggests that the 2 components of these heterogeneous groups of tumors were not derived from a common stem cell.<sup>12)</sup> The second theory is the hostage hypothesis, which proposes that non-neoplastic follicle cells are entrapped by medullary carcinoma and proliferate via trophic factor stimulation; genetic alterations during follicular cell proliferation lead to

neoplastic transformation.<sup>1,13)</sup> The third is the field effect theory, which proposes common neoplastic stimuli result in simultaneous transformation of follicular and parafollicular cells. In this case, although each carcinoma in the left thyroid gland was separated, with independent capsules, they were very close to each other and were multifocal. This might implicate a carcinogenic stimulus, as suggested by this theory. The fourth hypothesis is the collision theory, which suggests that 2 independent tumors are located in the same lesion by simple coincidence. Most reported cases could be explained by this theory, because papillary carcinoma incidence was high even in the general population and the coexistence of 2 carcinomas was separately identified in the thyroid in most cases, reflecting their different origins.

Although the exact pathogenesis of these cases is unknown, we suspect that concurrent papillary and medullary carcinoma incidence will increase consistently with the increasing rates of thyroid carcinoma diagnosis and surgery.<sup>2)</sup> Given the aggressive nature of medullary carcinoma and the inaccuracy of aspiration cytology for its diagnosis, some authors recommended routine examination of calcitonin and/or carcinoembryonic antigen levels when evaluating thyroid nodules.<sup>7)</sup> However, this should be more rationalized, in terms of relatively low incidence of medullary carcinoma and cost effectiveness, particularly under the national medical insurance system of the Korea. Therefore, pathologists should pay closer attention to histopathological examination and acknowledge the need for immunohistochemical staining to avoid missing additional lesions even in the presence of clearly visible well-differentiated thyroid carcinoma.

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