



Combined Squamous Cell Carcinoma and Follicular Carcinoma of the Thyroid

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Primary squamous cell carcinoma of the thyroid (PSCCT) is a malignant epithelial tumor, composed entirely of cells with squamous differentiation and accounting for fewer than 1% of all malignancies of the thyroid gland.¹ Because squamous cells are absent from the normal thyroid gland, the etiology of PSCCT remains unclear. Hypotheses include the differentiation of squamous cells derived from embryonic remnants of epithelial cells in the gland, squamous metaplastic changes in response to inflammatory diseases such as thyroiditis, and malignant neoplasms, such as papillary, follicular, or anaplastic carcinoma.² Occasionally, PSCCT arises from other thyroid diseases such as Hashimoto's thyroiditis, tall cell variant papillary carcinoma, follicular carcinoma, and anaplastic carcinoma.^{3,4} We describe a patient with the combination of a well-differentiated squamous cell carcinoma and follicular carcinoma of the thyroid. To our knowledge, this is the third report of a patient with primary squamous cell carcinoma plus follicular carcinoma of the thyroid in the English language literature.^{2,5}

CASE REPORT

A 69-year-old man visited Asan Medical Center for dysphagia and a gradually growing huge anterior neck mass of 10 years duration. He had no clinical symptoms related to thyroid dysfunction and had been repeatedly treated at another institution with radiofrequency ablation for his cystic neck lesion. Fine nee-

dle aspiration cytology at that time showed squamous cells and many inflammatory cells, leading to a diagnosis of branchial cleft cyst. Neck computed tomography on this occasion showed a 13×11 cm cystic lesion with irregularly thick walls involving the left lobe of the thyroid gland; the lesion also contained a strongly enhanced solid portion, septation, and calcification (Fig. 1A). Fusion whole body positron emission tomography fluorine-18 fluorodeoxyglucose was performed, showing abnormal uptake only by the neck mass (Fig. 1B). The esophagus, stomach, and larynx were unremarkable on esophagogastroduodenoscopy. The patient underwent total thyroidectomy with neck lymph node dissection. Macroscopically, a huge mass measuring 14×13×8 cm had replaced the entire left lobe of his thyroid gland, with the mass also involving the right lobe. Multiple cystic spaces measuring up to 8.2 cm in the greatest dimension were present in the central portion of the mass and were filled with dirty necrotic fluid. The solid part of the mass was well demarcated, round in shape and had tan, firm, and smooth cut surfaces. Although the mass abutted the thyroid capsule, there was no extension to the surrounding soft tissues or other organs (Fig. 1C). The tumor consisted histologically of two well-delineated components. The center contained a cystic lesion lined by atypical squamous epithelium. The squamous cells showed unequivocal pleomorphism and extensive keratinization, resulting in a diagnosis of squamous cell carcinoma with cystic degeneration (Fig. 2A). The peripheral part of the mass was composed of a solid growth of thyroid follicles. The two components were in direct contact, but they did not show areas of transition (Fig. 2B). The follicular lesion was cellular and displayed microfollicular and trabecular growth patterns. The follicle cells contained abundant eosinophilic cytoplasm and mildly atypical round nuclei with smooth contour. Small nucle-

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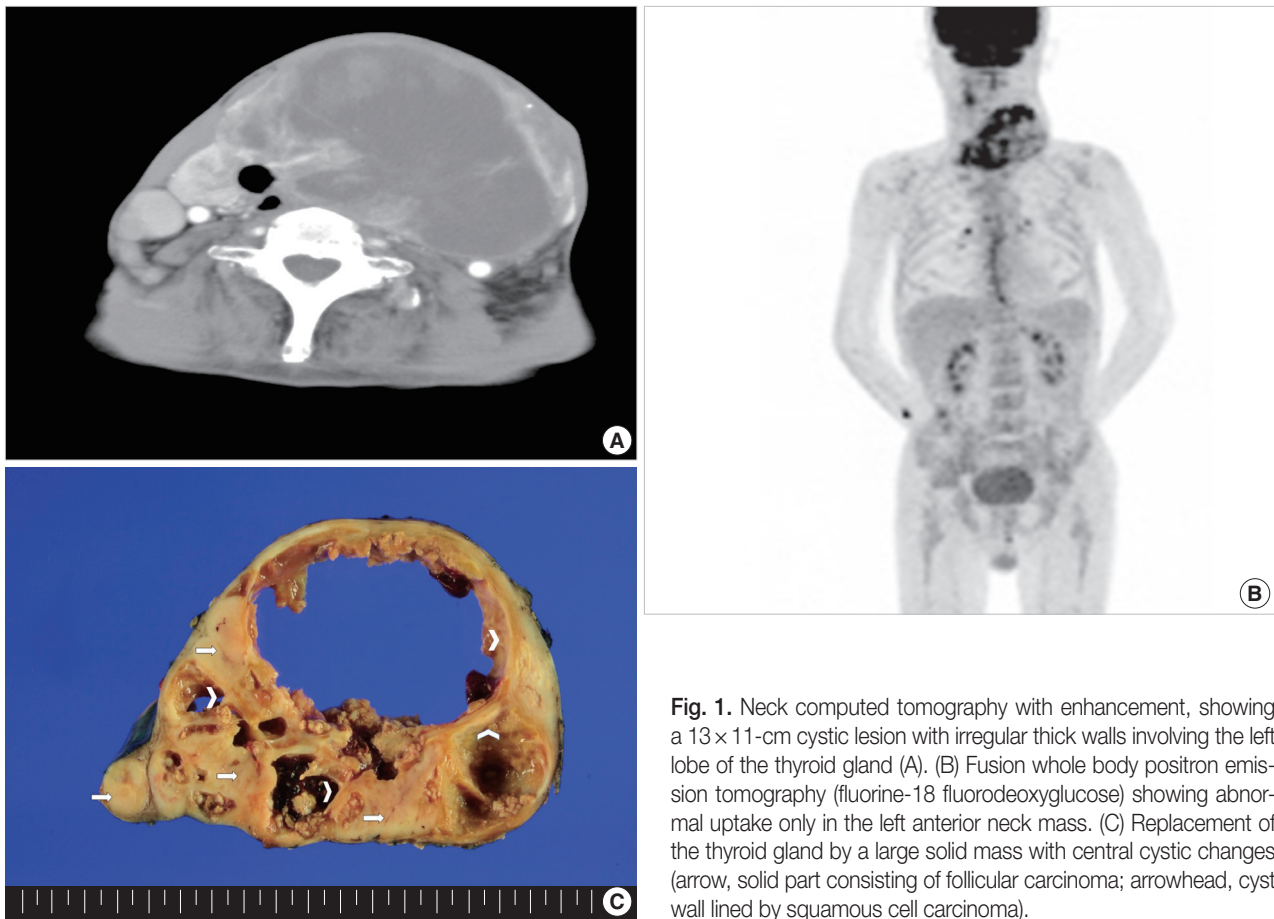


Fig. 1. Neck computed tomography with enhancement, showing a 13 × 11-cm cystic lesion with irregular thick walls involving the left lobe of the thyroid gland (A). (B) Fusion whole body positron emission tomography (fluorine-18 fluorodeoxyglucose) showing abnormal uptake only in the left anterior neck mass. (C) Replacement of the thyroid gland by a large solid mass with central cystic changes (arrow, solid part consisting of follicular carcinoma; arrowhead, cyst wall lined by squamous cell carcinoma).

oli were frequently seen, whereas mitotic figures were rare (Fig. 2C). The peripheral boundary of the follicular lesion was surrounded by a thick fibrous capsule, and showed a generally expansile, but partly invasive, growth pattern (Fig. 2D). Immunohistochemical examination showed that the squamous cell carcinoma was positive for p63, thyroid transcription factor 1 (TTF-1), and p53 and had a 20% Ki-67 labeling index (Fig. 3A–E). The follicular carcinoma component was diffusely positive for galectin-3 (Fig. 3I), TTF-1, and CD56 (Fig. 3F) and negative for p53, cytokeratin 19 (Fig. 3G), and HBME-1 (Fig. 3H), and the Ki-67 labeling index was 2%. Of the 18 dissected cervical lymph nodes, none was found to contain a metastatic tumor. The patient was lost to follow up 1 month later, but Korean National Health Insurance data show that he survived for 15 months after surgery.

DISCUSSION

We describe a patient with a combined squamous cell carcinoma and follicular carcinoma of the thyroid. Because one of

these components was observed on aspiration cytology and the other by core needle biopsy, a preoperative diagnosis could not be determined. The resected tumor also required detailed consideration. Differential diagnoses included anaplastic transformation from a follicular carcinoma, metastatic squamous cell carcinoma to a follicular carcinoma, follicular carcinoma with squamous differentiation, and primary thyroid squamous cell carcinoma intermingling with follicular carcinoma.

Patients with anaplastic carcinoma usually present with a rapidly growing neck mass and have a median survival of 6 months.⁶ Histologically, anaplastic carcinomas tend to show widely invasive growth, extensive tumor necrosis, marked nuclear pleomorphism, and high mitotic activity. When anaplastic carcinomas show squamoid differentiation, squamoid cells are usually mixed with spindle or giant cells.⁶ Our patient had a slow growing neck mass and mild to moderate cellular atypia without giant cells, spindle cells or atypical mitoses. Moreover, keratinizing squamous cell nests were in contact with the follicular carcinoma without transitional areas.

Metastasis to the thyroid gland is rare, with fewer than 2% of

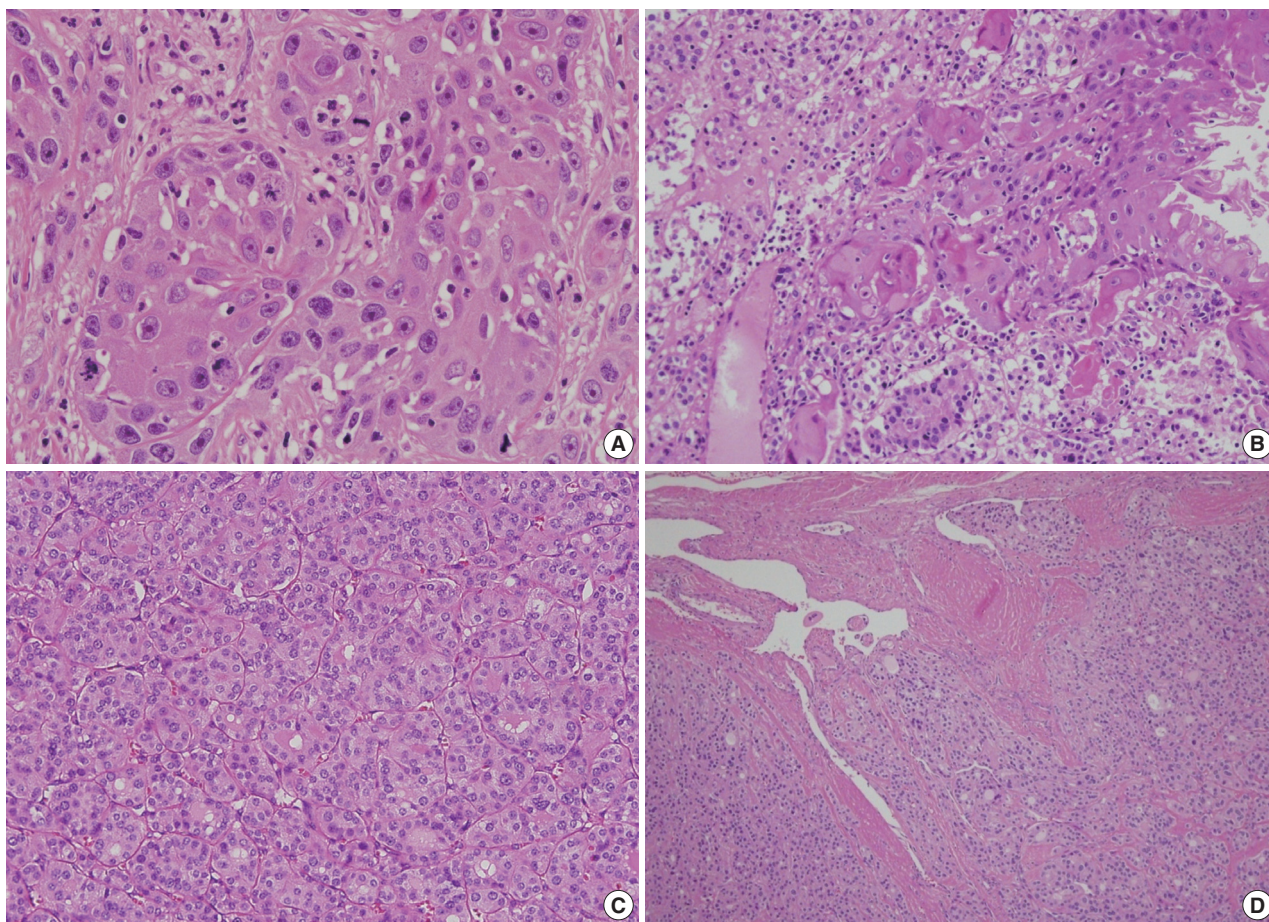


Fig. 2. Histologic examination of the mass, showing it is composed of a cystic zone lined by a well-differentiated squamous cell carcinoma (A) and a solid zone consisting of an invasive follicular carcinoma (C, D). (B) The squamous cell carcinoma nests are in direct contact with the follicular carcinoma, but the two elements are well distinguished.

thyroid tumors being metastatic squamous cell carcinomas to the thyroid gland.⁷ Metastases to the thyroid gland generally develop within two years of identification of the primary site.⁸ Our patient showed no evidence of squamous cell carcinoma of non-thyroidal origin. Squamous metaplasia has been reported from both benign and malignant thyroid lesions, including Hashimoto's thyroiditis, follicular adenoma, and papillary thyroid carcinoma,^{3,9} but there are no reports of squamous metaplasia transforming into squamous cell carcinoma in thyroid tissue. In many cases, the *de novo* appearance of primary squamous cell carcinoma from follicular epithelium without prior metaplastic change is considered likely.¹⁰ Our patient showed no evidence of squamous metaplasia, and the border between the two components was abrupt. Overall features of the case led to a diagnosis of PSCCT combined with follicular carcinoma.

PSCCT is reported to have an aggressive clinical course, similar to that of anaplastic carcinoma. However, the two prior case

reports of mixed squamous cell carcinoma and follicular carcinoma of the thyroid showed less aggressive courses. One report described a 56-year-old man with a hoarse voice and a rapidly growing mass over 3 months on the right side of the thyroid gland. The resected 3-cm thyroid mass was found to be a well differentiated squamous cell carcinoma intermingled with follicular carcinoma. Metastatic follicular carcinomas were found in the left upper lung and T7 spine at that time and 7 years later, respectively, but the patient survived more than 8 years after surgery.⁵ The other patient was a 67-year-old man with a 6 months history of progressive enlarging anterior neck mass. A right lobectomy was performed, yielding an 8-cm mass. Histologic examination showed a poorly differentiated squamous cell carcinoma mixed with follicular carcinoma. Despite the development of a metastatic follicular carcinoma in the right iliac crest 3 years after surgery, the patient survived more than 6 years after surgery.² The different biologic behaviors displayed by PSCCT

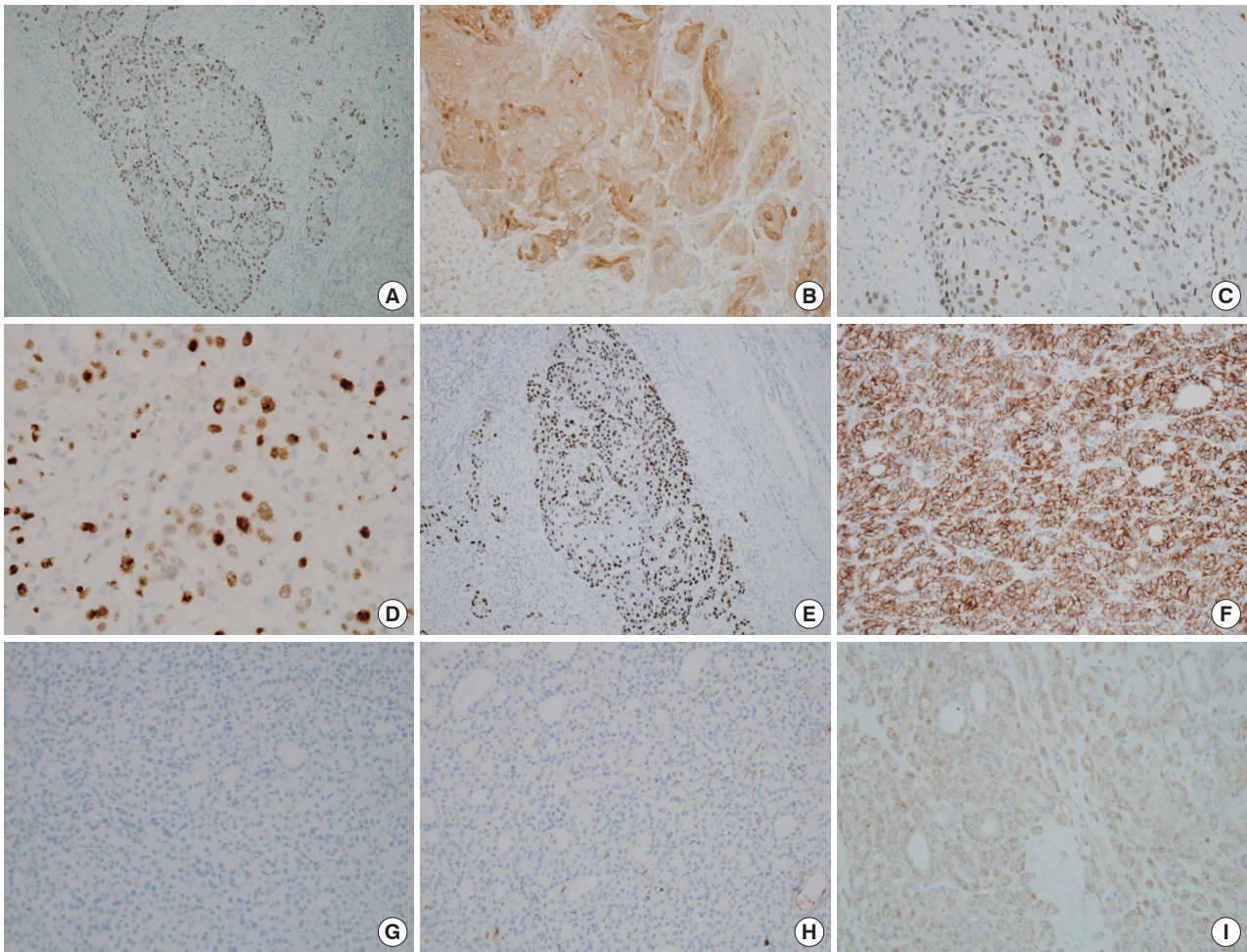


Fig. 3. Immunohistochemical staining of portions of the mass. The squamous cell carcinoma is positive for p63 (A), galectin-3 (B), thyroid transcription factor 1 (C), and p53 (E), and had a Ki-67 labeling index of 20% (D). The follicular carcinoma is diffuse positive for CD56 (F) and galectin-3 (I) and negative for cytokeratin 19 (G) and HBME-1 (H).

and mixed squamous cell carcinoma and follicular carcinoma are not fully understood, but they could be related to the presence of follicular carcinoma as a barrier. It is noteworthy that the metastatic diseases in both cases involved follicular carcinoma alone. Our patient could have undergone a similar clinical course but died 15 months after surgery of unknown cause.

In summary, we have described a patient with mixed squamous cell carcinoma and follicular carcinoma of the thyroid gland, including a discussion of its histogenesis and clinical differences from PSCCT.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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