A Rare Case of Coexistence: Papillary Thyroid Carcinoma Dedifferentiated to Squamous Cell Carcinoma: A Case Report

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Abstract

Background: Squamous cell carcinoma (SCC) of the thyroid is a rare condition comprising less than 1% of all thyroid malignancies. Thyroid SCC is a variant of undifferentiated thyroid carcinoma and is also associated with the tall-cell variant of papillary thyroid carcinoma (PTC) and spindle cell carcinoma. Given its aggressive clinical course, early recognition of the disease is essential to management.

Case: We report a rare case of a 67-year-old, Filipino male initially presenting with an anterior neck mass over a period of 11 months. This was accompanied by compressive symptoms, anorexia, and easy fatigability. He underwent total thyroidectomy with histopathology consistent with diffuse sclerosing variant of PTC with squamous differentiation. The patient had rapid tumor growth, tumor recurrence, nodal metastasis, and invasion of local structures within a year after his initial presentation. He underwent completion thyroidectomy and selective neck dissection and concurrent chemo-radiotherapy with a course of radiation (60 Gy in 33 fractions) and chemotherapy with Carboplatin and Paclitaxel. After 13 months of initial presentation, the patient eventually succumbed to cardiac arrest.

Conclusion: This transformation of the thyroid is an aggressive malignancy with increased mortality; hence it should be considered in cases presenting with progressive clinical behavior. Due to his aggressive disease, the patient's nutritional status, airway protection, and immunity were compromised. A combined modality with surgery, radiotherapy, and chemotherapy to prevent disease progression may be needed due to its aggressive clinical course.

Keywords: Papillary thyroid carcinoma with squamous differentiation, aggressive thyroid carcinoma, case report

Introduction

Squamous cell carcinoma (SCC) of the thyroid is a rare condition because there is no squamous epithelium in a normal thyroid gland.[1,2,4,5] However, these squamous cells may represent embryologic remnants, inflammatory conditions such as Hashimoto's thyroiditis or adenomatous goiter, and rarely carcinoma.[2,4,6] This aggressive carcinoma comprises less than 1% of all thyroid malignancies.[1,2]

This malignant squamous cell transformation is hypothesized to have been "dedifferentiated" from the aggressive well-differentiated thyroid carcinomas, secondary to chronic thyroid gland inflammation.[1,4] Thyroid SCC is a variant of undifferentiated thyroid carcinoma and is also associated with the tall-cell variant of papillary thyroid carcinoma (PTC) and spindle cell carcinoma.[1,3]

These rare subtypes of thyroid carcinoma remain to have a poor prognosis and aggressive course. Similar transformations had been reported but this remains an area of investigation since there is no consensus on treatment due to its rarity.[4,6]

Case

A 67-year-old, Filipino male, presented with a painless neck mass over a period of 11 months. He was clinically euthyroid. He had no known thyroid disorder and had no family history of malignancy. The patient had a 15-pack-year smoking history and had no known exposure to any chemical or radiation. He was a retired police officer.

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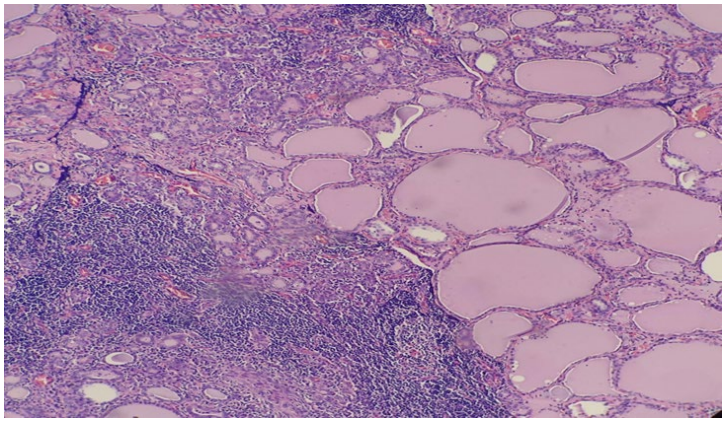

Figure 1A. Thyroid microsections disclose malignant neoplasm composed of infiltrative small thyroid follicles. Tumor nests appear solid with background changes of chronic lymphocytic thyroiditis.

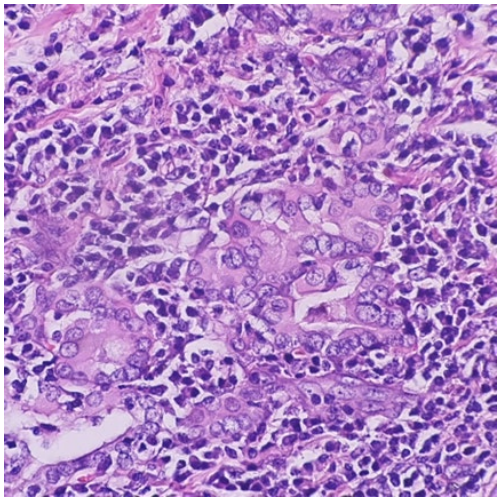

Figure 1B. High power magnification showing characteristic nuclear features of PTC (nuclear grooves, chromatin margination with prominent nucleoli, Orphan Annie nuclei).

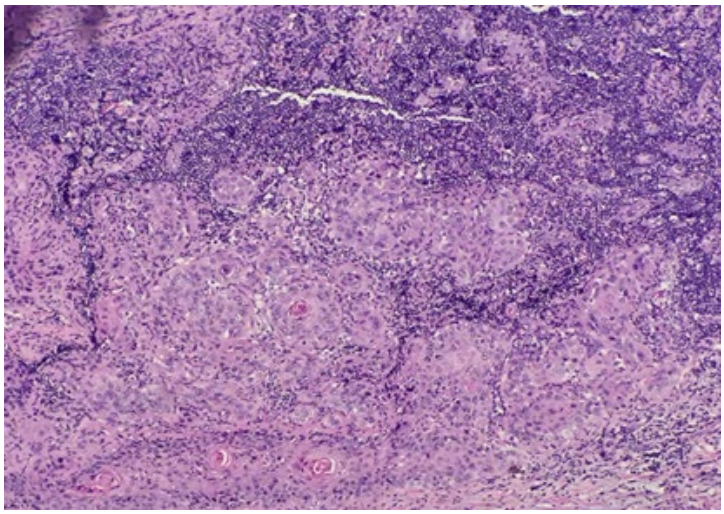

Figure 1C. Other portions show extensive involvement of thyroid gland, with tumor nests appearing solid and having features of squamous metaplasia.

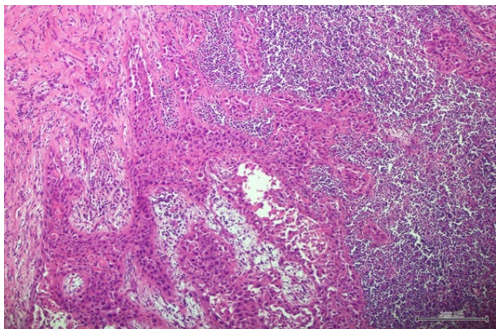

Figure 1D. Left paratracheal tissue. Microsections disclose a malignant neoplasm composed of highly atypical epithelial cells forming infiltrative sheets and cords.

Initial clinical examination showed an enlarged thyroid gland, soft, non-tender with no palpable cervical lymph node. Neck ultrasound demonstrated an enlarged thyroid gland with a hypoechoic left thyroid nodule (1.9 x 1 x 1.2 cm). Ultrasound-guided fine needle aspiration biopsy of the described nodule showed a colloid nodule. No further management was done until four months later, the patient then manifested with increased tumor growth, with an anterior neck mass of approximately 4 x 4.5cm with no palpable cervical lymph node, accompanied by compressive symptoms such as dysphagia, shortness of breath, and anorexia

He underwent total thyroidectomy with histopathology consistent with diffuse sclerosing variant of PTC with squamous differentiation, arising from chronic lymphocytic thyroiditis with extra-thyroidal extension (Fig. 1A,1B). The left thyroid lobe tumor was 4.5cm in its greatest dimension. Immunohistochemical markers showed (+) TTF-1, (+) HBME-1 and (+) PAX – 8. Levothyroxine supplementation was given post-total thyroidectomy with a TSH target of < 0.1 IU/mL. The patient did not develop any significant hypocalcemia post-operatively and Vitamin D levels were within normal range.

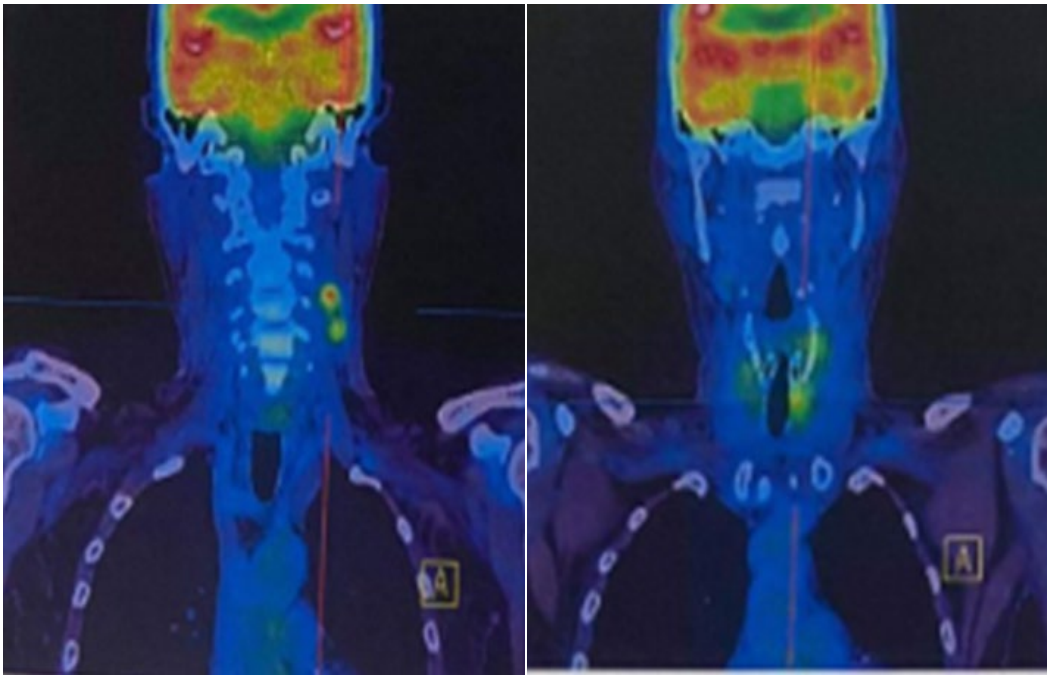

Figure 2A. 18F-FDG PET/CT scan showing (a) prominent lymph nodes (at least 2 FDG-avid noted) seen along left side of neck (level III) with SUVs up to 8.5; (b) FDG-avid focus in left thyroid bed with SUV max of 6.8.

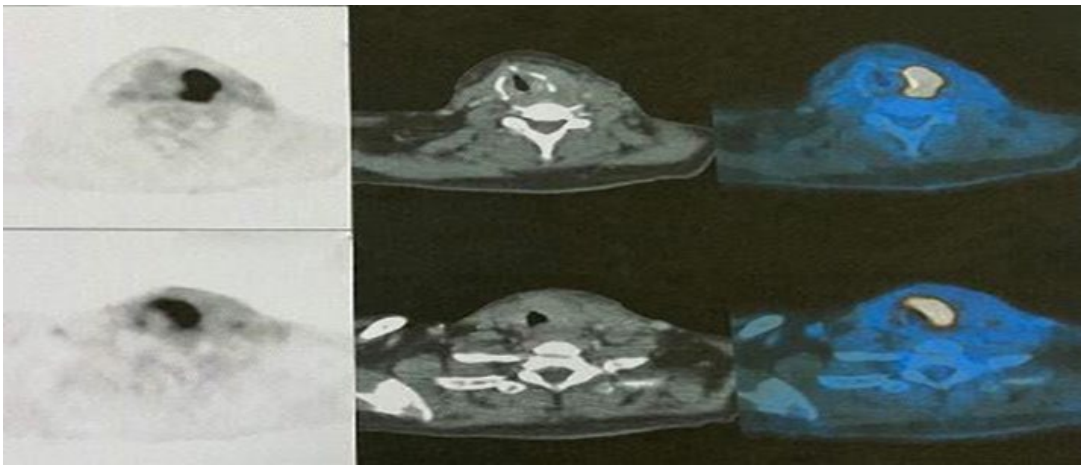

Figure 2B. 18F-FDG PET/CT scan demonstrating large enhancing mass (SUV max up to 23.8) with ill-defined margins and hypodense centers in the left thyroid bed, extending superiorly at the level of the larynx (approx. 6.1 x 3.5 x 3.5 cm).

Two months after total thyroidectomy, he noticed a palpable, firm, non-tender left cervical lymph node (Level III) approximately 1 x 2 cm and hoarseness of voice. No laryngoscopy was performed at that time. Positron emission tomography (PET) scan showed hypermetabolism in the thyroid bed and tumor recurrence with 2 FDG-avid lymph nodes, on Level III with SUVS up to 8.5 (Fig. 2A). Radioactive iodine (RAI) imaging showed functioning thyroid tissues.

The patient had completion thyroidectomy with selective neck dissection within 3 months after the initial surgery. Histopathology revealed keratinizing squamous cell carcinoma metastatic to lymph nodes in Levels II, IV and paratracheal lymph nodes (*Figure 1C,1D*). Molecular studies were not pursued by the patient. Repeat PET/CT scan showed rapid tumor recurrence in the left thyroid bed with strap muscle and thyroid cartilage infiltration, as well as cervical lymph node invasion (*Figure 2B*).

Treatment goals included local and systemic control of the disease, improvement in his nutritional status and airway patency, and enhanced quality of life. The patient did not receive radioactive iodine therapy. Percutaneous endoscopic gastrostomy (PEG) insertion and prophylactic tracheostomy addressed nutritional status

and airway protection, respectively. He was maintained on 1-2 LPM oxygen per tracheostomy due to intermittent episodes of shortness of breath. Because of his decreased appetite and dysphagia, enteral nutrition through PEG feeding was provided. He was treated with a course of external beam radiation (60 Gy in 33 fractions) and had concurrent chemotherapy with Carboplatin-Paclitaxel regimen for two cycles. During his treatment, the patient experienced side effects such as fatigue, odynophagia, dryness in the mouth, and decreased appetite. The patient's treatment response was primarily monitored clinically with minimal improvement in his airway. During the entire course of treatment, the patient and relatives were aware of the prognosis and complications of this rare disease. After 13 months of initial presentation, patient eventually died.

Discussion

We presented a case of an aggressive papillary thyroid carcinoma with squamous transformation, which is a rare subtype of thyroid carcinoma described only in case reports.[3] Papillary thyroid carcinoma is the most common thyroid malignancy with a 10-year survival rate of over 90%.[5] However, some variants of PTC have a more aggressive clinical course and carry a poor prognosis.

Given the clinical presentation and duration, differentials include the variants of PTC, poorly differentiated thyroid carcinoma, and anaplastic thyroid carcinoma.[7] The initial histopathologic finding revealed a diffuse sclerosing variant of PTC with squamous differentiation, arising from chronic lymphocytic thyroiditis. According to Hararah et al, the metaplasia theory postulates that chronic inflammation, such as Hashimoto's thyroiditis, can lead to squamous metaplasia.[1] Like the findings of Basnet et al., LiVolsi and Merino, squamous cell carcinoma appears because of metaplasia of follicular epithelial cells.[3,8] The study of Evans stated that there is a close histologic association between papillary and squamous cells and that SCC cells were in 'close apposition' with tall-cell variant cells.[9]

Within months after the patient's initial surgery, there was metastasis to the cervical lymph nodes which revealed to be a keratinizing squamous cell carcinoma. This is an aggressive type of thyroid carcinoma wherein patients can present with an invasion of local structures, extrathyroidal extension, or nodal metastasis at presentation.[10] Similar to the study of Kleer et al., 6 of 8 patients had metastasis to the cervical lymph nodes.[7] LiVolsi's study showed that the tumors of SCC and the tall-cell variant of PTC were aggressive and had an extrathyroidal extension and vascular invasion.[8]

Molecular studies were not pursued by the patient. Kleer et al. suggested that the detection of p53 tumor suppressor gene and Ki-67 antigen by immunohistochemistry may have a role in predicting prognosis but this remains an area of investigation.[7,9] Immunohistochemistry can elucidate typical cytokeratin pattern (CK 5/6 and CK 7) which is important to exclude a squamous cell carcinoma derivative or if coexisting with PTC.[11] Genetic testing among family members is another area of investigation. Overall, due to the limitation of molecular studies in squamous cell thyroid carcinoma, there is no molecular evidence to draw conclusions on the molecular profiles.[12]

Since SCC of the thyroid has a high probability of recurrence and local invasion, total resection of the tumor tissue is needed.[4,10] No treatment guidelines have been established yet since there are only a few reported cases.[3,13] Management includes combined treatment with surgery and concurrent radiotherapy and chemotherapy to decrease disease progression and prevent local recurrence.[10] According to Thewjitcharoen et al., de-differentiated tumor cells become more resistant to conventional treatment, and prognosis worsens significantly.[5] Patient mortality can be secondary to the compression or direct invasion of the trachea.[10] Our patient underwent PEG insertion and prophylactic tracheostomy to address nutritional status and airway protection due to the invasion of the tumor.

This aggressive tumor also represents a clinical presentation similar to an anaplastic and spindle cell thyroid carcinoma.[3,5] Given the rapid course of disease recurrence and local invasion, early recognition of the disease is essential to allow prompt initiation of therapy. Clinicians should consider the possible transformation of PTC into more aggressive malignancies, in cases of unusual clinical behavior.[5,14,15] This squamous transformation of the thyroid is a malignancy with a poor prognosis with an average length of survival of less than a year.[10,13] Kitahara et al. reported a case of local recurrence as squamous cell carcinoma of the remnant thyroid four years after subtotal thyroidectomy due to PTC.[16] Due to the rarity of this disease, long-term follow-up and disease-free survival of these patients is another area of investigation.

Conclusion

This transformation of the thyroid is an aggressive malignancy with increased mortality; hence it should be considered in cases presenting with progressive clinical behavior. Due to his aggressive disease, the patient's nutritional status, airway integrity, and immunity were compromised. Combined modality with surgery, radiotherapy, and chemotherapy to prevent disease progression and local recurrence were needed. Due to its rarity, a multidisciplinary approach is necessary in the management although survival rate remains poor.

Conflict of Interest. The authors declare no conflict of interest relevant to this article.

References

1. Hararah KM, Gertz JR, Sippel SR, et al. De-differentiation of Conventional Papillary Thyroid Carcinoma into Squamous Cell Carcinoma. Thyroid Disorders Ther 2015;4: 192. doi:10.4172/2167-7948.1000192
2. Makay O, Kaya T, Ertan Y, Icoz G, Akyildiz M, et al. Primary Squamous Cell Carcinoma of the Thyroid: Report of Three Cases. Endocr J 2008; 55(2):359-64. doi: 10.1507/endocrj.k07e-102. Epub 2008 Apr 1.
3. Basnet A, Pandita A, Fullmer J, et al. Squamous Cell Carcinoma of the Thyroid as a Result of Anaplastic

Transformation from BRAF-Positive Papillary Thyroid Cancer. Case Reports in Oncological Medicine. 2017; 2017:4276435. doi: 10.1155/2017/4276435.

4. Beninato T, Kluijfhout W, Thurston F, et al. Squamous Differentiation in Papillary Thyroid Carcinoma: a Rare Feature of Aggressive Disease. Journal of Surgical Research, 223(2018), 39–45. doi: 10.1016/j.jss.2017.10.023
5. Thewjitcharoen Y, Krittiyawong S, Butadej S, et al. Dedifferentiation of Papillary Thyroid Carcinoma into Squamous Cell Carcinoma in an Elderly Patient – a Case Report. Medicine 2020; 99:16(e19892). http://dx.doi.org/10.1097/MD.0000000000019892
6. Hsieh M, Besch B, Peterson J. and Henson C. Primary Squamous Cell Carcinoma of the Thyroid Treated with Concurrent Chemoradiation and Palliative Immunotherapy: a Case Report. Journal of Medical Case Reports. 2022; 16:364. https://doi.org/10.1186/s13256-022-03596-0
7. Kleer CG, Giordano TJ, Merino MJ. Squamous Cell Carcinoma of the Thyroid: an Aggressive Tumor Associated with Tall Cell Variant of Papillary Thyroid Carcinoma. Mod Pathol 2000;13: 742-746. doi: 10.1038/modpathol.3880129.
8. LiVolsi VA and Merino MJ. Squamous Cell in the Human Thyroid Gland. Am J Surg Pathol 1978; 2:133– 40; DOI: 10.1097/00000478-197806000-00002
9. Evans W. De-differentiation of Papillary Thyroid Carcinoma into Squamous Cell Carcinoma. A Case of Coexistence within an Excised Neck Lesion. BMJ Case Rep 2012: bcr2012007707. doi: 10.1136/bcr-2012-007707.
10. Franco M, Oderay C, Sánchez-Vilar A, et al. Papillary Thyroid Carcinoma Associated to Squamous Cell Carcinoma. Endocrinol Nutr. 2014; 61:226-228. doi: 10.1016/j.endonu.2013.10.007. – from 9 to 10
11. Struller F, Senne M, Falch C, et al. Primary Squamous Cell Carcinoma of the Thyroid: Case Report and Systematic Review of the Literature. International Journal of Surgery Case Reports 37 (2017) 36–40. http://dx.doi.org/10.1016/j.ijscr.2017.06.011
12. Lam AK. Squamous Cell Carcinoma of the Thyroid: A Unique Type of Cancer in World Health Organization Classification. Endocrine-related Cancer 2020;27: R177-R192. https://doi.org/10.1530/ERC-20-0045.
13. Yan W, Chen H, Li J, Zhou R, Su J. Primary Squamous Cell Carcinoma of Thyroid Gland: 11 Case Reports and a Population-based Study. World Journal of Surgical Oncology 2022; 20:352 https://doi.org/10.1186/s12957-022-02814-9
14. Chongxi R. Papillary Thyroid Carcinoma Coexists with Undifferentiated Carcinoma & A Case Report and Review of Literature. SOJ Surgery 3(3): 1-3.
15. Lee JI, Chung YJ and Lee SY. Papillary Thyroid Carcinoma Recurring as Squamous Cell Carcinoma 10 years after Total Thyroidectomy: Lessons from Rapidly Progressive Papillary Thyroid Carcinoma. Intern Med 2013;52(14):1593-7. doi: 10.2169/internalmedicine.52.9310
16. Kitahara S, Ito T, Hamatani S, Shibuya K, Shiba T. Thyroid Papillary Carcinoma Recurring as Squamous Cell Carcinoma: Report of a Case. Surg Today. 2006;36(2):171-4. doi: 10.1007/s00595-005-3107-3.