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10th Gulf Week for Cancer Awareness Launches in Kuwait - February 2025 Focuses on 'Your Health is in Your Awareness'

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Case Report

Primary Squamous Cell Carcinoma of the Thyroid: A Rare Subtype of Anaplastic Carcinoma

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Abstract

Background: Primary squamous cell carcinoma of the thyroid is an uncommon neoplasm, recently redefined as a variant of anaplastic thyroid carcinoma (ATC). It has a dismal prognosis, with most patients succumbing to the disease within the first year following diagnosis. Due to its rarity, there are no well–established treatment guidelines.

Case Presentation: In this study, we report a new case of primary squamous cell carcinoma of the thyroid of the thyroid. The patient underwent total thyroidectomy with recurrent lymph node dissection with rapid local recurrence in less than 6 months without adjuvant therapy.

Discussion and Conclusion: This case highlights the aggressivity of this tumor and emphasizing the necessity of advancements in scientific research, particularly in genomics, with the aim of enhancing survival outcomes for patients with this rare malignancy.

Keywords: squamous cell carcinoma; thyroid gland; diagnosis; treatment

Introduction

Primary squamous cell carcinoma of the thyroid (SCCTh) is an extremely rare tumor, accounting for less than 1% of thyroid tumors. Previously considered a separate entity, SCCTh has been reclassified as a subtype of anaplastic thyroid carcinoma (ATC) in the 5th edition of the WHO classification of thyroid malignancies. This tumor is highly aggressive, with a poor prognosis and rapid loco–regional progression [1,2].

Currently, there is no standardized treatment protocol, and management typically involves a multimodal approach, including surgery, radiotherapy, and systemic therapies such as targeted therapy and chemotherapy. However, no standardized therapeutic strategy has yet been established. Emerging genomic insights and prospective multicenter trials hold promise for optimizing the management of these ultra–rare malignancies [2,3].

In this report, we present a new case of primary squamous cell carcinoma of the thyroid, illustrating the tumor's aggressiveness and underscoring the urgent need for multicenter clinical trials to develop effective treatment strategies.

Case Presentation

This case involved a 54–year–old female patient, married with three children. Symptoms began one year before her first consultation, with the appearance of a cervical mass progressively increasing in volume, accompanied by moderate dyspnea. The condition evolved in a context of asthenia, but the patient's general condition remained stable. Cervical ultrasound revealed a multinodular goiter containing a large, hypoechoic, heterogeneous macro–

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nodule measuring 67×58×50 mm in the lower right lobe, with irregular contours, invasion, and thrombosis of the right internal jugular vein. A cervical CT scan further identified a large right lobo–isthmic thyroid mass measuring 56×60×42 mm, in close contact with the trachea, compressing and displacing it to the left (Figure 1). The mass encased the right jugulo–carotid vessels and the subclavian vein and extended into the superior anterior mediastinum (Figure 2). The larynx and hypopharynx appeared normal, with no evidence of cervical lymphadenopathy. Pan–endoscopic examination confirmed tracheal compression without tumor infiltration. The patient underwent total thyroidectomy with recurrent lymph node dissection.

Histopathological analysis revealed massive infiltration of both thyroid lobes by a poorly differentiated carcinomatous proliferation composed of cellular cords and clusters. The tumor cells were medium to large in size, with abundant eosinophilic cytoplasm, large hyperchromatic nuclei, and marked anisocytosis, along with numerous mitotic figures. Tumoral vascular emboli were observed, accompanied by capsular invasion of the thyroid gland (Figure 3). The tumor was 1 mm from the surgical margin. Lymph node dissection yielded three lymph nodes, all metastatic, with capsular rupture (03N+/03N). Immunohistochemical analysis showed positivity for CK (AE1/AE3), confirming epithelial origin, and strong diffuse positivity for P40 and P63 (Figure 4 & 5), confirming squamous differentiation. Conversely, thyroid markers TTF1 and thyroglobulin were negative. CK7 was positive, while CK20 was negative. To exclude secondary thyroid involvement, a complete clinical examination and upper aerodigestive tract assessment were performed, both of which yielded normal results. A thoraco–abdominopelvic CT scan was also unremarkable. Based on clinical, endoscopic, imaging, and immunohistochemical findings, primary squamous cell carcinoma of the thyroid was confirmed.

Following discussion at a multidisciplinary tumor board meeting, adjuvant radiotherapy was recommended. However, the patient refused treatment and was lost to follow–up. Four months later, she returned with a large cervical mass. A new cervical CT scan revealed a large, anterior lower cervical tumor, lateralized to the right, located at the thyroidectomy site and extending into the superior anterior mediastinum. The tumor measured 62×47×68 mm, encasing the cervical vessels. The lesion was deemed unresectable, and the patient was referred for combined radio–chemotherapy.

Discussion and Conclusion

Primary squamous cell carcinoma of the thyroid (SCCTh) is a rare malignancy, representing less than 1% of malignant tumors of the thyroid gland. It often occurs in elderly women,

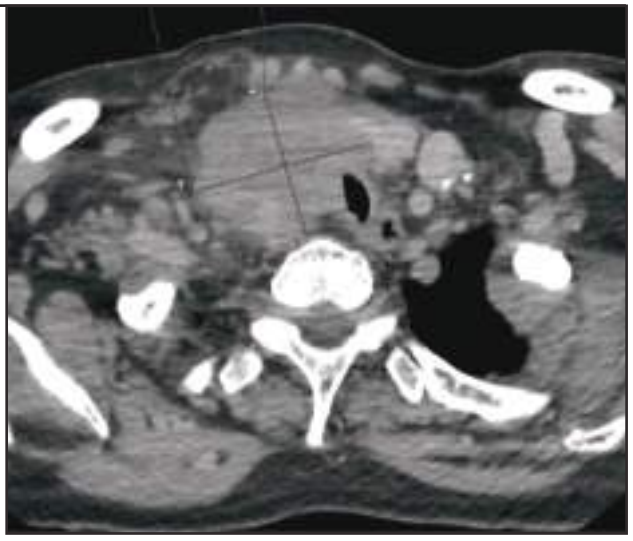


Figure 1: Right thyroid lobo–isthmic mass measuring 56x60x42mm, involving the right jugulo–carotid vessels and the subclavian vein.



Figure 2: The mass of the thyroid gland is compressing and pushing back the trachea to the left and is protruding into the upper mediastinum.

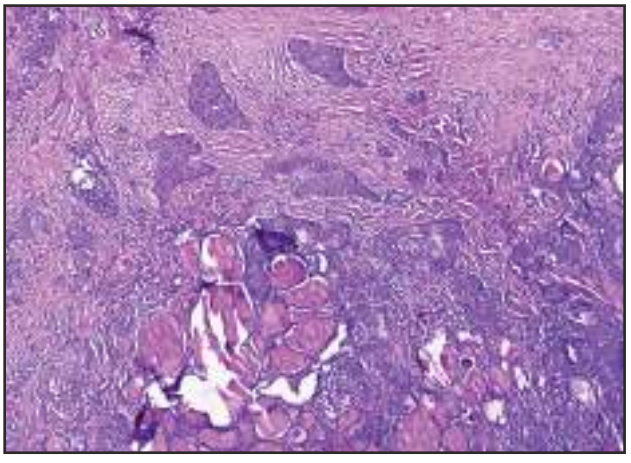


Figure 3: Microphotography shows irregular nests and cords of malignant epithelial cells with pleomorphic nuclei, prominent nucleoli, and abundant eosinophilic cytoplasm, invading the thyroid parenchyma. Desmoplastic stroma is observed. (HE ; 200X).

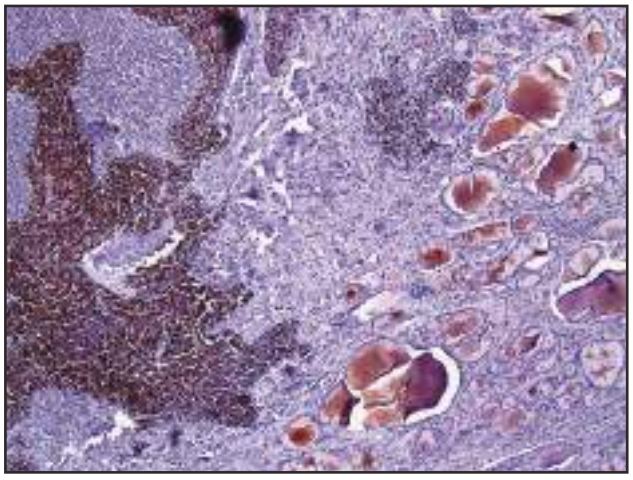


Figure 4: Microphotography shows nuclear staining of tumor cells by p40 antibody. (Anti–p40 ;200X).

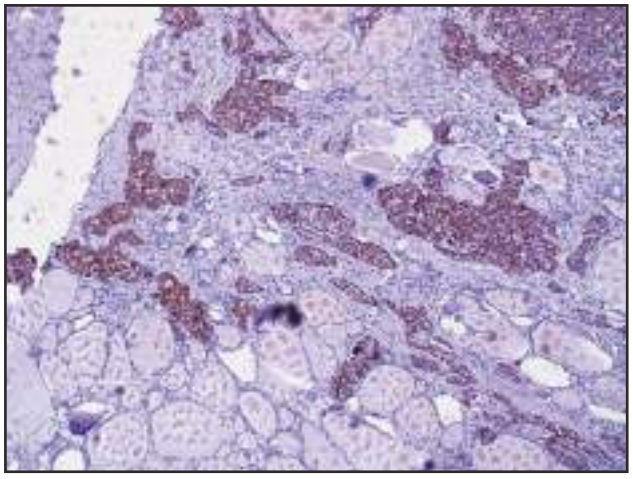


Figure 5: Microphotography shows nuclear staining of tumor cells by p63 antibody. (Anti–p63 ; 200X).

generally between 50 and 60 years of age, with a female–to–male ratio ranging from 1.37 to 2.5 [1]. According to the 2022 World Health Organization (WHO) classification of thyroid tumors, SCCTh has been reclassified as a subtype of anaplastic thyroid carcinoma (ATC) [2,3].

The initial step for any clinician faced with SCC of the thyroid should be to rule out either metastatic thyroid involvement from a distant cancer or loco–regional extension of cancer from adjacent aerodigestive tract organs (trachea, esophagus). Secondary SCC of the thyroid is ten times more common than primary SCC of the thyroid [4]. A recently published case highlighted the usefulness of 18F–FDG PET/CT in distinguishing between primary and secondary SCCTh and in staging [5]. In our patient, pan–endoscopy revealed no tumour infiltration of the trachea or other aerodigestive tract organs. Radiological exploration also showed tracheal deviation without infiltration. No primary tumor was found on clinical or radiological assessment.

The confirmatory diagnosis relies on immunohistochemical analysis, complementing morphological findings. In most cases, primary SCCTh is poorly differentiated, unlike other SCCs of the aerodigestive tract, which are often moderately differentiated. This may be considered in the etiological orientation during histological examination (primary vs. secondary SCC). PAX–8 is a key marker that suggests thyroid origin in SCC, with 91% of SCCTh cases expressing PAX–8. The markers p63 and p40 are specific for squamous differentiation. Regarding cytokeratin profiling, SCCTh is typically positive for CK 5/6, 7, and 19 and negative for CK 20 and CK 10/13. P53 overexpression found in 75% of cases, reflects tumor aggressiveness. However, SCCTh rarely expresses thyroglobulin and TTF–1 [6]. Few molecular biological data are currently available. The only gene studied in SCCTh is BRAF, with mutations found in more than 70% of cases [7].

SCCTh is an aggressive tumor with a poor prognosis, with most patients dying within one year of diagnosis. Its prognosis closely resembles that of anaplastic thyroid carcinoma, with rapid loco–regional invasion and a high local recurrence rate. More than 50% of patients die within six months of diagnosis, and the one–year survival rate is only 33.3% [1,8]. Therefore, most authors recommend an aggressive multimodal treatment, including surgery, radiotherapy, and systemic therapy. Cho JK et al. were the first to publish a meta–analysis on SCCTh treatment outcomes and prognostic factors. However, their study was limited due to data heterogeneity and an insufficient number of cases to draw firm conclusions [9].

Surgery remains the cornerstone of SCCTh treatment. Complete resection with clear surgical margins is crucial, as margin quality significantly influences local relapse–free survival. Surgery should be radical, extend to adjacent invaded structures and be accompanied by lymph node dissection [1]. Unfortunately, due to locally advanced disease at diagnosis, complete resection is often difficult. In our patient, although resection was complete, the margin was only 1 mm, which was insufficient.

Due to the rarity of this tumor, there is no consensus on adjuvant therapy. Adjuvant treatment is usually indicated in cases of non–radical surgery, while its role after complete resection remains unclear. A 2022 study including 314 SCCTh patients showed no survival benefit from adjuvant therapy following complete resection [10]. However, given the high rate of early loco–regional recurrence, most studies suggest systematic post–operative radiotherapy to improve local control. Therefore, adjuvant radiotherapy should be discussed within a multidisciplinary tumor board. Radiotherapy remains the treatment of choice for unresectable tumors, often combined with concurrent

chemotherapy. Some case reports have shown that cisplatin–based chemoradiotherapy improves local control and overall survival in non–operable patients [1,9].

Regarding chemotherapy, none of the published systemic agents have shown clear efficacy in SCCTh management. However, advances in molecular biology suggest that targeted therapy could improve survival through personalized treatment approaches. In anaplastic thyroid carcinoma, a study evaluated BRAF/MEK inhibition in BRAF V600E–mutated patients [11]. Given that BRAF V600E mutations are found in 70%–87% of SCCTh cases, Brandenburg T et al. tested dabrafenib and trametinib in a patient with BRAF–mutated SCCTh, leading to a good response and improved quality of life for over 12 months [12].

However, few studies have explored immunotherapy for SCCTh due to its rarity. Hsieh ML and al. reported a case where a patient, initially treated with exclusive radio–chemotherapy, developed pulmonary metastases six months after treatment and was placed on pembrolizumab. The response was heterogeneous, with regression of lung metastases but continued thyroid tumor progression [13].

Across all published clinical cases and small series, SCCTh prognosis remains extremely poor. Some researchers have developed nomograms to predict prognosis and guide personalized treatment decisions. Tian et al. analyzed 218 SCCTh cases from the SEER database, developing a reliable and effective nomogram for predicting SCCTh prognosis, which may assist clinicians in decision–making [14].

The rarity of this tumor makes it difficult to standardize its management. Indeed, the treatment of SCCTh remains poorly defined. However, the recent integration of SCCTh into the spectrum of ATC could encourage research, particularly in molecular biology. Thus, early detection of mutations could help guide targeted and personalized therapy. On the other hand, the role of immunotherapy remains unclear.

Funding and Conflict of Interest

The authors declare no conflict of interest.

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