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Sclerosing Mucoepidermoid Cancer: A Unique Entity

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Abstract

Sclerosing mucoepidermoid thyroid cancer (SMECE) is a rare entity with less than 100 cases reported in the literature. Previously considered to have an indolent course, however, recent evidence has reported an aggressive nature ranging from local invasion to distant metastasis. We present a 66-year-old Caucasian female with SMECE who initially presented neck compressive symptoms. A thyroid ultrasound (US) revealed a solid hypoechoic mass replacing the left thyroid lobe. Fine needle aspiration cytology (FNAC) of the nodule resulted in suspicion of Papillary Thyroid Cancer, Bethesda category 5. The patient underwent total thyroidectomy and surgical pathology showed SMECE. Post-therapy whole-body scan following treatment with 150 mCi I-131 showed no residual or metastatic disease. SMECE is more common in females, between the third to eighth decade of life. Preoperative diagnosis may not be accurate given variable cytopathologic features. Differential diagnoses include primary squamous cell carcinoma of the thyroid, squamous differentiation of other thyroid malignancies, anaplastic thyroid cancer and nodular sclerosing variety of Hodgkin's lymphoma. Due to its rarity, treatment of SMECE has ranged from thyroid surgery without or with radioactive iodine therapy, to surgery and external beam radiation and even chemotherapy.

Keywords

Sclerosing Mucoepidermoid Cancer, Papillary Thyroid Cancer, Thyroid Cancer

1. Introduction

Sclerosing mucoepidermoid cancer with eosinophilia of the thyroid (SMECE) is a rare entity with less than 100 cases reported in the literature [1]. Initially described by Chan *et al.* in 1991, [2] it was included as a separate entity by the World Health Organization in 2004. [3] The latest 2022 WHO classification of

endocrine and neuroendocrine tumors classifies SMECE as a new category "thyroid tumors of uncertain histogenesis", whereas in 2017 WHO classification, it came under salivary gland type carcinomas of the thyroid gland. [4] Previously considered to have an indolent nature, recent evidence has reported an aggressive nature ranging from local invasion to distant metastasis. The evidence from the literature is mainly in the form of case reports and case series. The largest case series reviewed 61 cases, with 2 notable cases with BRAF V 600 mutations. The authors emphasized BRAF V600 mutation as a marker of aggressive forms of SMECE and the utility of targeted molecular therapy for SMECE treatment. [5] Another large case series concluded distinct molecular markers in SMECE as compared to other thyroid cancer specifically lack of expression of thyroglobulin in SMECE, p53 expression in 100% cases, variable expression of TTF-1, and lack of MAML2 expression distinguishing it from salivary gland mucoepidermoid carcinomas. [6] Management usually includes tumor resection with or without lymph node dissection and adjuvant therapy in case of extensive disease. We present a case of a female with SMECE treated with total thyroidectomy and radioactive iodine therapy. We then summarize the literature on SMECE.

2. Case Presentation

A 66-year-old Caucasian female presented to her primary care physician for an annual wellness visit with 6 months of neck compressive symptoms including mild dysphagia and globus sensation. Thyroid ultrasound showed a solid hypoechoic mass, 8.2 × 5.3 × 5.9 cm replacing the left thyroid lobe with an additional solid hypoechoic nodule 2.2 × 1.1 × 1.6 cm in the isthmus region (**Figure 1**). A neck ultrasound was negative for pathologic-appearing lymph nodes. Past medical history was significant for invasive ductal carcinoma of the breast (in

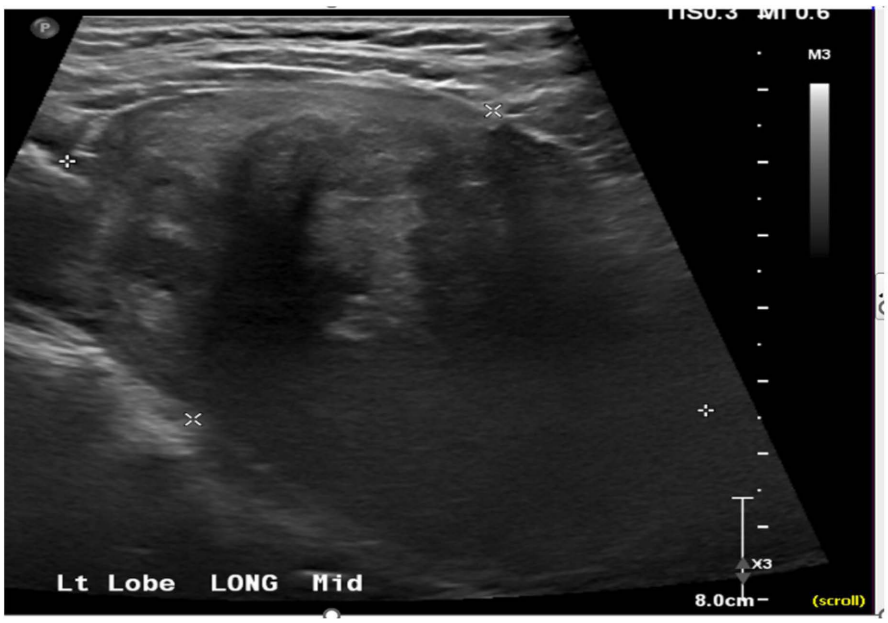

Figure 1. Solid hypoechoic mass replacing left thyroid lobe.

remission). There was no personal history of neck irradiation and no family history of thyroid cancer. Physical exam showed stable vitals with BMI 35.8 Kg/m^2. There was no evidence of thyroid enlargement or palpable masses in the neck on physical exam.

3. Diagnostic Assessment

Thyroid function test showed TSH - 4.5 (0.5 - 4 mIU/ml) (4.5 mIU/L), FT4 - 1.31 (0.7 - 1.9 ng/dl) (16.89 pmol/L). Thyroid US as described above. Computerized tomography (CT) of the chest with contrast confirmed an enlarged thyroid gland with asymmetric enlargement of the left thyroid lobe with a large hypoechoic nodular component extending caudal, below the level of the clavicle and sternum measuring approximately 6.4 × 6.9 × 7.7 cm and mass effect on the trachea (Figure 2). FNAC of the left thyroid mass reported Bethesda category 5, suspicious for papillary thyroid cancer.

4. Management and Follow-Up

The patient underwent a total thyroidectomy. Central or lateral neck dissection was not performed. Surgical pathology of the left thyroid lobe showed SMECE, measuring 8.6 × 6.9 × 5.8 cm, pT4aNxMx, with positive margins for tumor, and no angiolymphatic invasion. Additionally, there was a 0.3 cm right-sided papillary microcarcinoma (follicular variant) with chronic lymphocytic thyroiditis. Histology showed infiltrative nests of squamous/epidermoid cells and cystic glandular components lined by monocytes with clear to foamy-appearing cytoplasm on a background of fibrotic stroma (**Figures 3-6**). The patient was initiated on a suppressive dose of levothyroxine to target TSH <0.1 mIU/ml, considering the high risk of recurrence. Postoperative thyroglobulin was <1 ng/ml (0 - 115 ng/ml) (<1 ug/L) with antithyroglobulin antibodies <0.1 IU/ml (< 1.6 - 55 IU/ml) (<0.1 kIU/L). Three months after surgery, the patient received radioiodine ablation with

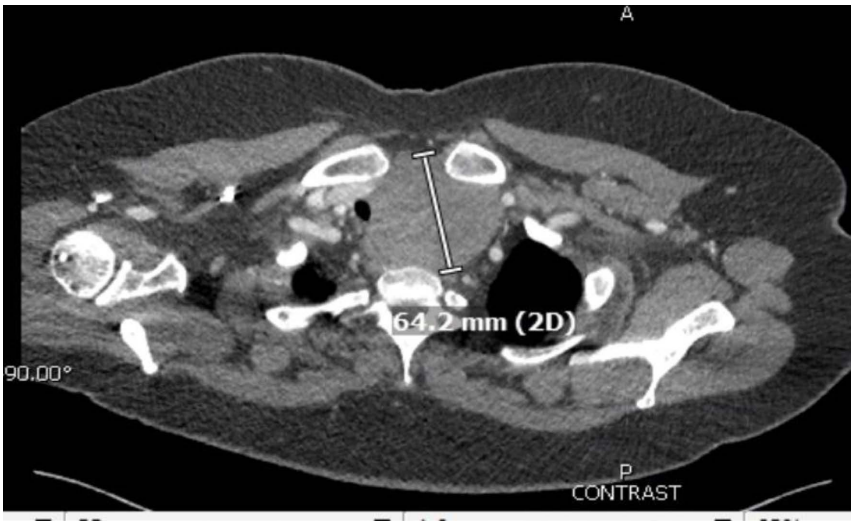

Figure 2. Left thyroid mass compressing the trachea.

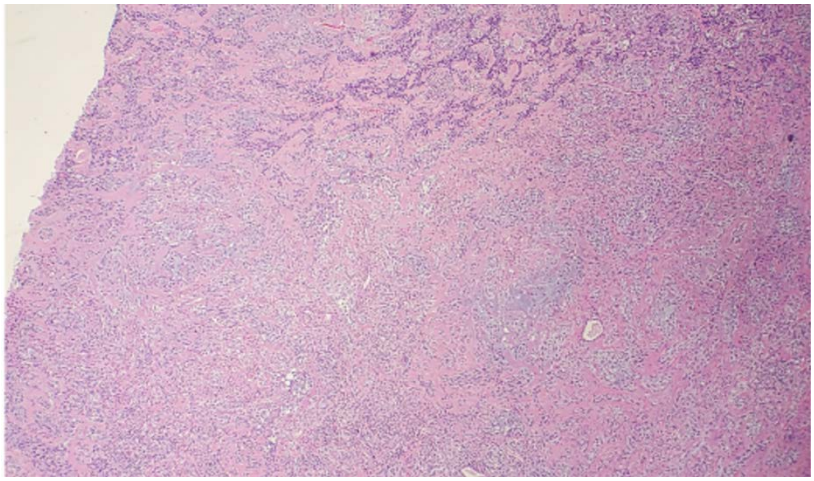

Figure 3. Low-power image shows infiltrative tumor cells in a heavily fibrotic stroma with a biphasic appearance.

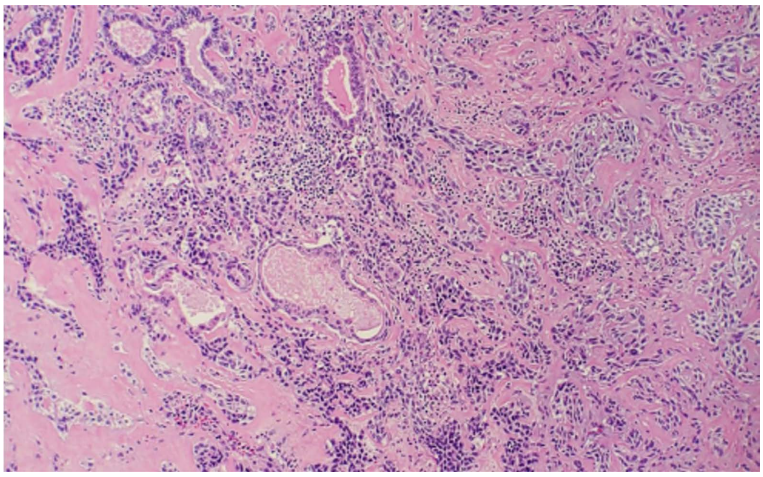

Figure 4. Medium power image with infiltrative squamous\ epidermoid cells with cystic glandular areas in the heavily fibrotic stroma.

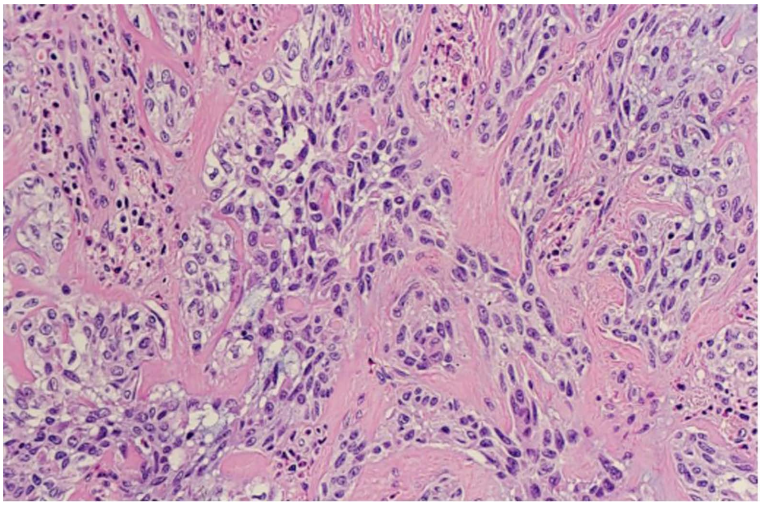

Figure 5. High power image shows the infiltrative squamous\epidermoid cells, scant mucocytes with clear to foamy-appearing cytoplasm, and scattered eosinophils.

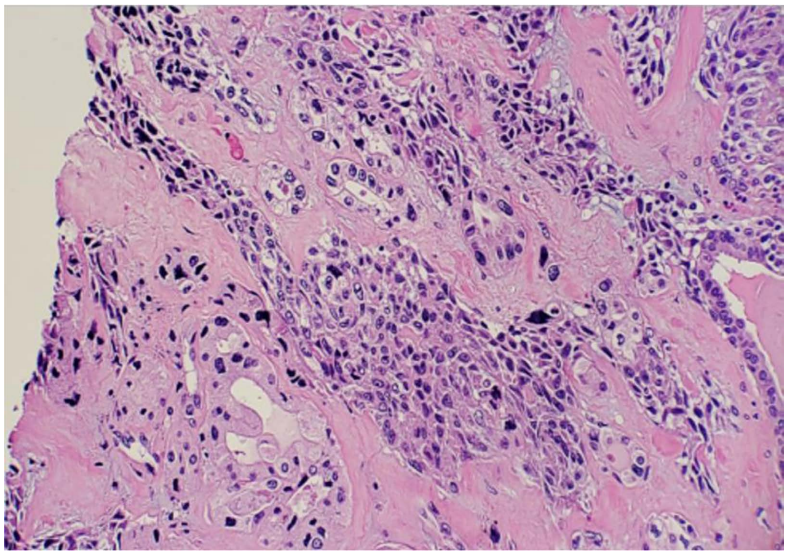

Figure 6. High power image shows the infiltrative nests of squamous\epidermoid cells and cystic glandular component lined by mucocytes with clear to foamy-appearing cytoplasm.

150 mCi of I-131. Post-therapy whole-body scan showed no residual/metastatic disease. Notably, CT scan of the chest with contrast preoperatively showed punctate calcified granuloma at left lung base in addition to a non-calcified 7 mm nodule. The patient is being followed with periodic CT chest imaging to monitor the 7 mm nodule. Given the lack of thyroglobulin expression by SMECE in literature, we are not monitoring thyroglobulin levels. We continue to follow our patient with periodic neck ultrasounds and CT chest as the lungs are the most common site of metastasis.

5. Discussion

SMECE is one of the rare types of thyroid carcinomas. It is hypothesized to be derived from the ultimobranchial body. [6] An alternative theory about its origin is from metaplastic cells from chronic lymphocytic thyroiditis. [6] It is more common in females in their 3rd-8th decade of life, with an average age of presentation 55 years. [1] The most common presentation is unilateral painless thyroid mass. The average size of these tumors was noted to be 4.5 cm in a case series, with largest size of 13 cm on presentation. [5] SMECE usually presents as solid hypoechoic masses with variable borders and calcification. SMECE appeared as a hypoechoic lobulated mass, similar to imaging characteristics of thyroid lymphoma and intrathyroidal thymic carcinoma on ultrasound in a case series. [7]

Histologically, SMECE has stromal sclerosis with epidermoid and glandular differentiation with eosinophilic and lymphocytic infiltration. [8] Coexistent chronic lymphocytic thyroiditis and papillary thyroid cancer are frequently identified. Pre-operative cytological diagnosis may not be accurate due to variable features. [2] Positive thyroglobulin washout may not be very helpful in excluding SMECE preoperatively given co-existing papillary thyroid cancer.

Although different from other thyroid carcinomas in terms of mutations, there are no consistent molecular characteristics of SMECE. SMECE usually shows positive staining for cytokeratin. It shows negativity for thyroglobulin expression, and variable TTF-1 expression making it distinct from papillary thyroid cancer. [3] [4] It was also MAML2 negative in a study, distinguishing it from salivary gland tumors. [3] Recent evidence suggesting an association of BRAF V600 with advanced cases of SMECE may support early testing for BRAF V600 mutation in these cases. [5] Positive staining for p63 may indicate an origin from solid nest cells/ultimobranchial body.

An important differential diagnosis of SMECE is Mucoepidermoid carcinoma (MEC), as both tumors share histological features like epidermoid/squamous cells and mucocytes in clusters with variable stroma. Co-existing lymphocytic thyroiditis in the background is more commonly associated with MEC than SMECE. [8] Other differences include larger epidermoid cell sheets, cystic spaces, and the absence of vascular invasion. [9]

Other differential diagnoses of SMECE include primary squamous cell carcinoma of the thyroid, squamous differentiation of other thyroid malignancies like papillary thyroid cancer, medullary thyroid cancer, anaplastic thyroid cancer, nodular sclerosing variety of Hodgkin lymphoma, thyroid malignancies with thymic differentiation, and Langerhans cell histiocytosis. The absence of frequent mitoses, atypia, and presence of sclerosis with eosinophilia differentiate squamous cell thyroid cancer from SMECE. Similarly, the absence of Reed Sternberg cells and CD15, CD30, and CD 45 positivity in SMECE distinguishes it from the nodular sclerosing variety of Hodgkin's lymphoma, especially in the case of nodal metastasis. [9] SMECE lacks the characteristic nuclear features of the diffuse sclerosing variant of papillary thyroid cancer. Medullary thyroid cancer shows positive staining for calcitonin and the absence of eosinophilia which are absent in SMECE. [5] Thyroid malignancies with thymic differentiation lack mucocytes and significant eosinophilia and staining positive for BCL-2, CD 5, and CD 117. [2] There are case reports on co-occurrence of SMECE with anaplastic thyroid cancer [10].

Routine follow-up for common thyroid malignancies like papillary thyroid cancer involves monitoring of thyroglobulin levels. This is not a good tumor marker for SMECE due to the lack of thyroglobulin expression by SMECE. As SMECE is a rare malignancy, there are no established tumor markers yet in the literature for follow-up of this entity.

In the review of 61 cases, the gross extrathyroidal extension was seen in 54%, lymph node metastasis in 40% and distant metastasis in 15% of cases with distant metastasis most commonly seen in the lungs. [5] The first case of SMECE with renal metastasis has also been recently reported. [5] In one case series review, local recurrence was seen in 33% of cases with a mean time to recurrence of 2.3 years in 24 cases. [6] In the same series, metastasis occurred in 29% of cases with the mean time to metastasis being 2.4 years from the time of diagnosis. The use of BRAF inhibitors was suggested for the treatment of SMECE, given

recent reports of BRAF V600 positivity in 2 advanced cases of SMECE. [5]

Outcome data available from 40 cases in a case series showed 23% people died and 63% of patients were alive disease free during the follow-up. [5] Given recent evidence of an aggressive nature, close monitoring is advised.

To conclude, SMECE is a rare cancer and can have an aggressive biology. Preoperative diagnosis based on FNA may not be reliable given variable cellular features. There is no established tumor marker yet for SMECE, BRAFV600 may indicate the aggressive form of cancer. Follow-up mainly includes imaging like ultrasound and CT neck and chest for periodic monitoring for metastasis. No established treatment strategy exists or has been addressed in guidelines due to a small number of reported cases, however, treatment ranges from only thyroid surgery to thyroid surgery with radiation ± chemotherapy and radioactive iodine. The effectiveness of these treatments has not been studied given the rarity of SMECE.

Clinical suspicion should be high for SMECE in patients with chronic lymphocytic thyroiditis with atypical features of tumor on surgical pathology. If clinical suspicion remains high for this entity, an aggressive approach should be followed from the beginning. There is a need for more research looking into the utility of targeted molecular therapy in aggressive cases of SMECE. The prognosis remained unknown and is usually determined by the extent of cancer spread.

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Author Contributions

AM composed the manuscript and literature review. AM, CD, GJ and FH were responsible for the acquisition, analysis, or interpretation of data for the work, revising it critically for important intellectual content, and giving final approval of the version to be published. All authors contributed to the article and approved the submitted version.

Informed Patient Consent for Publication

Signed informed consent was obtained directly from the patient.

Data Availability

Original data generated and analyzed during this study are included in this published article.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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