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Case Report

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S100-negative secretory carcinoma of thyroid, mimicking papillary thyroid carcinoma: a diagnostic pitfall resolved by next generation sequencing

Abstract

Secretory thyroid carcinoma (STC) is an extremely rare disease and demonstrates the ETV6-NRK3 fusion gene. The majority of the cases have cribriform to solid architecture with eosinophilic cells and intraluminal secretion and immunohistochemistry staining with S100, GATA-3, mammoglobin and negative for PAX-8 and TTF-1. We present a challenging case of Secretory Carcinoma of the thyroid with PTC-like nuclear features and S100 negativity.

Keywords: head and neck, endocrine thyroid, secretory carcinoma

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Introduction

Secretory thyroid carcinoma (STC) is an extremely rare disease that has been described in fewer than ten cases. The majority of these cases have occurred in middle-aged females.[1] STC is hypothesized to originate from ectopic salivary gland remnants, but the initiating molecular event is the t(12;15)(p12;q25) translocation, which leads to the ETV6-NTRK3 gene fusion. This fusion creates a constitutively activated tyrosine kinase with further transformation capabilities that have been linked to several types of malignancies.[2]

STCs morphologically resemble papillary thyroid carcinomas with oncocytic features, but immunohistochemical stains and molecular testing can help elucidate the final diagnosis.[1] This case report describes the process of discovering and working up a difficult case of secretory thyroid carcinoma.

Case Presentation

The patient is a 63-year-old female with a remote history of breast cancer status post mastectomy, Hashimoto's thyroiditis, and anxiety who initially presented to her primary care provider with hoarseness, dyspnea on exertion, and nasal congestion. She was given conventional medications for seasonal allergies and asthma, but her symptoms progressed over the course of two years to the point that she had to sleep sitting upright at night. Eventually, she was seen by an otolaryngologist who noted left vocal cord paralysis and subglottic stenosis on scope exam, concerning for a mass. A CT scan noted a 5.8 x 3.7 x 2.9 cm heterogeneous, hypodense mass arising from the left lobe of the thyroid, causing mass effect against the trachea. A Fine Needle Aspiration (FNA) was performed, which was interpreted as atypia of undetermined significance. The patient then underwent surgery to remove the obstructing lesion and relieve the airway. She was found to have an exophytic, non-friable mass protruding into the airway from the left side of the trachea. In addition, there was an endotracheal mass that was interpreted as papillary thyroid carcinoma on frozen section.

When permanent sections were analyzed of the left-sided lesion, it was noted that there was cribriform architecture on histology concerning for an adenocarcinoma. Immunohistochemistry stains were conducted, which were positive for PAX8 in the tumor cells and negative for TTF-1, S100, and thyroglobulin. GATA3 was weakly positive. A diagnosis of adenocarcinoma, not otherwise specified, was favored (Figure 1– Figure 5).

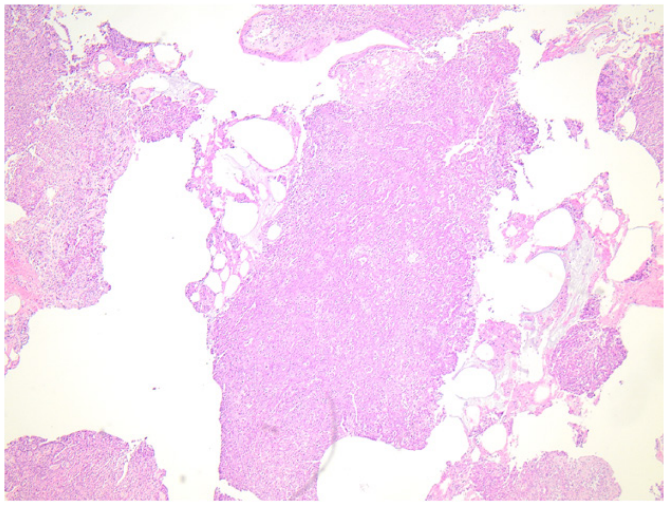

Figure 1 Low magnification: 40X Cribriform patter.

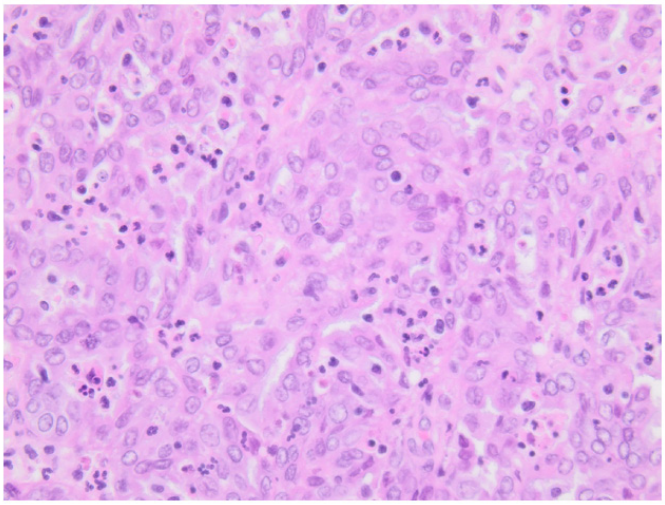

Figure 2 High magnification: 400X

Elongated vesicular nuclei, with nuclear grooves (mimics papillary thyroid carcinoma nuclear features).

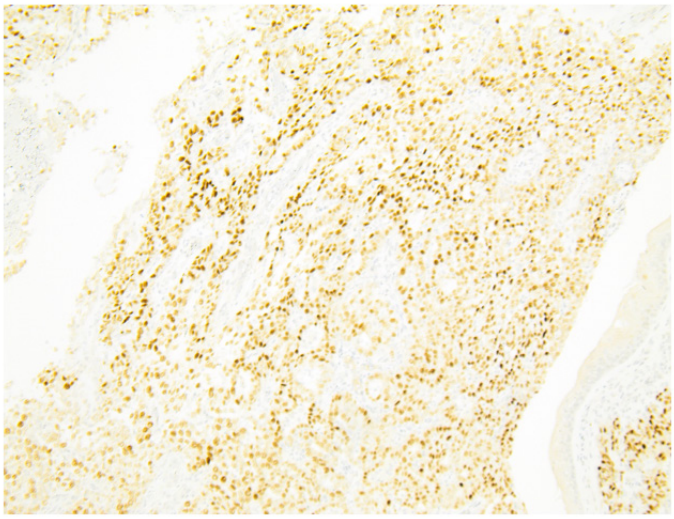

Figure 3 PAX-8: Positive.

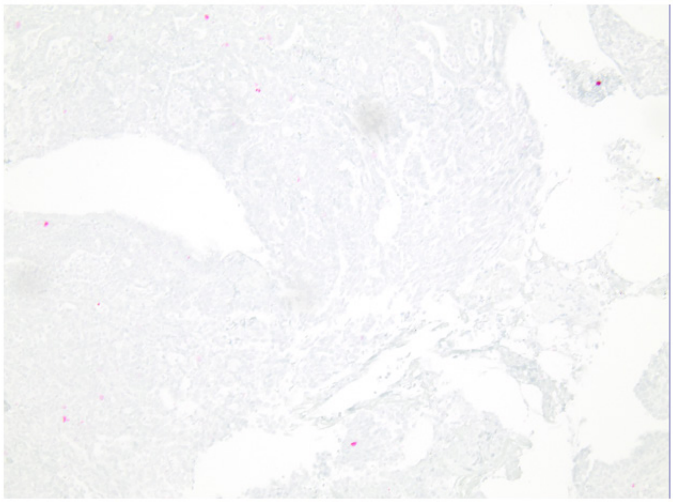

Figure 4 S100: Negative.

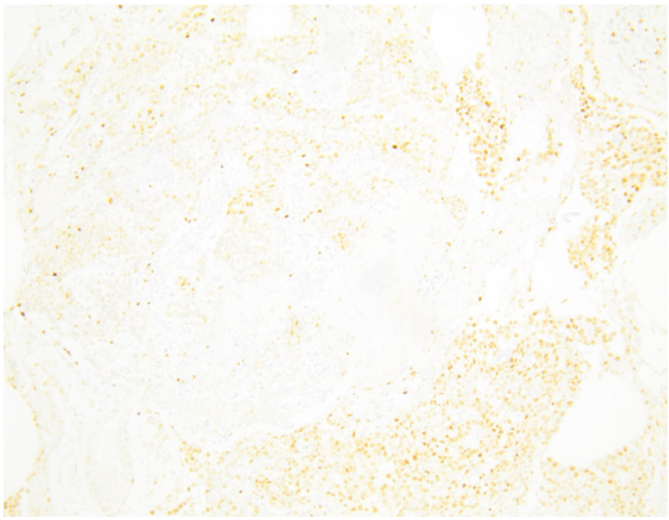

Figure 5 GATA-3: Patchy positive.

Next-generation sequencing was performed at Caris Life Sciences at the clinician's request, and the sample was positive for an ETV6:NTRK3 fusion. This molecular alteration is most frequently associated with secretory carcinoma, so this became the new favored diagnosis. The patient began larotrectinib and is currently receiving radiation therapy.

Discussion

Secretory thyroid carcinoma is an exceptionally rare malignancy of the thyroid gland first described in 1997. STC can often resemble mammary analog secretory carcinoma (MASC) found in salivary glands and breast tissue. It is also known to mimic other subtypes of thyroid carcinoma.

The present case contributes to the growing body of literature on STC by highlighting its diagnostic challenges. As observed in this case, STC presents with vague symptoms, including a palpable mass, hoarseness, dysphagia, and dyspnea due to mass effect. The patient in this report presented with a neck mass, and on initial imaging, the lesion appeared nonspecific. Fine needle aspiration (FNA) biopsy results were also inconclusive, which aligns with the diagnostic difficulties frequently encountered with STC.

Histologically, STC is characterized by the presence of cells that form solid sheets and nests, exhibiting abundant eosinophilic cytoplasm with areas of necrosis. Immunohistochemically, tumor cells typically express markers such as mammaglobin, and cytokeratins, which can aid in distinguishing STC from other thyroid carcinomas. In the present case, the tumor was negative for typical stains diagnostic of thyroid carcinomas such as TTF-1 and thyroglobulin, providing a diagnostic clue to the entity. Notably, STC can also produce a mucin-like secretory product, giving it the oncocytic features noted in this case.

Similar to previously reported cases of STC, this case demonstrated a poorly differentiated neoplasm with eosinophilic cells and cribriform architecture. Morphologically, a variable architecture of papillary, micropapillary, and cribriform patterns with secretions throughout the neoplasm can be helpful for considering STC in the differential diagnosis. However, the presence of papillary and micropapillary patterns raises the diagnostic pitfalls of oncocytic papillary thyroid carcinoma and poorly differentiated thyroid carcinoma.[3,4,5] Immunohistochemical stains are of variable use in these cases, as STC demonstrates variable S100 and GATA3 staining in the literature.[3,4,5] TTF-1 is negative in STC, but its expression can also be lost in dedifferentiated PTC and anaplastic thyroid carcinoma.[6] Therefore, molecular analysis becomes imperative in confirming the diagnosis of STC.

Primary secretory carcinomas of the breast and salivary gland should also be considered in the differential diagnosis, especially in this case, where the patient had a history of primary breast carcinoma. Secretory carcinoma of the breast also demonstrates the ETV6-NRK3 fusion gene, but the majority of these cases are positive for GATA3 and S100 on immunohistochemistry.[7] Similarly, primary secretory carcinoma of the salivary gland will have the same gene fusion, but a majority of these neoplasms will positively stain for SOX10 and MUC4 on immunohistochemistry.[7] Therefore, a thorough immunohistochemical workup and clinical history are necessary to make a final diagnosis.

Surgical resection remains the primary treatment modality for STC, with total thyroidectomy being the standard approach. In some cases, radioactive iodine (RAI) therapy may be considered postoperatively,

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though its efficacy in STC remains uncertain due to the lack of iodine avidity in some tumors.

The rarity of STC poses significant challenges in treatment decision-making, particularly because it does not follow the typical behavior of more common thyroid malignancies. Given that STC can sometimes behave aggressively and present with regional metastasis, close monitoring postoperatively is crucial.

Conclusion

This is a complicated case of secretory carcinoma that required next-generation sequencing to reach the final diagnosis after surgical removal. Early recognition and surgical intervention are imperative for better prognostic outcomes, but it is important to maintain a broad differential diagnosis in the workup of thyroid nodules with unusual morphology. The chronology and results of this case serve as an important reminder of the importance of utilizing tools such as genomic testing in scenarios where histologic diagnoses are unclear.

Acknowledgments

None.

Conflicts of interests

The authors declare that there are no conflicts of interest.

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