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A case of primary secretory carcinoma of the thyroid with high-grade features

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Sir

We report a case of primary secretory carcinoma of the thyroid with high-grade features to highlight cytological and histological clues to the diagnosis. The diagnosis of primary secretory carcinoma of the thyroid is challenging, due both to the fact that it has only recently been described and because of its morphological overlap with papillary thyroid carcinoma (PTC); however, differentiating secretory carcinoma from PTC is crucial both for prognostication and treatment purposes.

A 58-year-old woman presented to an outside hospital with progressive hoarseness. Imaging studies demonstrated a 4-cm thyroid nodule that spanned the left lobe with potential impingement of the left recurrent laryngeal nerve (Figure 1). A fine-needle aspiration (FNA) was interpreted as suspicious for PTC. A subtotal thyroidectomy was performed. Based on the presence of tumour necrosis and a high proliferative index, the tumour was diagnosed as poorly differentiated thyroid carcinoma. The patient was referred to our institution for treatment, at which point the pathology was re-reviewed. The aspirate was cellular, and showed small sheets of tumour cells with a moderate amount of cytoplasm, nuclear enlargement, clearing and some nuclear contour irregularities and grooves. The nucleoli were prominent and located centrally. Many of the cells had a signet-ring-cell morphology with intracytoplasmic vacuoles. The cell block demonstrated similar cytological features as seen in the aspirate, but in addition, a cribriform architecture was appreciable along with luminal colloid-like secretory material. The cytological findings are shown in Figure 2. Histologically, the tumour was infiltrative and associated with abundant hyalinized stroma. There was extensive lymphovascular invasion and extrathyroidal extension, and a broad

Ethics statement

The study has been performed according to the Declaration of Helsinki. The procedures have been IRB-approved (protocol no. 2016P001885). Informed consent was not required for our study.

Conflict of interest

The authors have no conflicts of interest.

front of tumour was present at margin. In the context of the operative report noting that tumour grossly involved the trachea, the findings were consistent with T4a disease. Lymph nodes were negative for tumour. The tumour had a predominantly cribriform and microcystic architecture with associated colloid-like material. Focally, the tumour showed papillary and micropapillary growth, with adjacent multilayered epithelium. The tumour cells were uniform and had a moderate amount of eosinophilic cytoplasm. Many of the cells demonstrated intracytoplasmic vacuoles with eosinophilic material, correlating with the signet-ring cell morphology seen on the FNA. The nuclei were enlarged with vesicular chromatin and a prominent, eosinophilic central nucleolus. Nuclear contour irregularities and grooves were striking in some areas of the tumour. Pseudoinclusions were not identified. Mitoses were seen throughout the tumour [mitotic count was up to seven per 10 high-power fields (HPFs)], and tumour necrosis was present. The background thyroid showed chronic lymphocytic thyroiditis. The histological features are depicted in Figure 3. The tumour was positive for PAX8, but negative for TTF-1 and thyroglobulin. The Ki67 proliferative index was approximately 20%. Based on recent reports of secretory carcinoma of the thyroid and the resemblance of the tumour to secretory carcinoma of the salivary gland,¹⁻⁵ additional immunohistochemical stains were performed revealing that the tumour was diffusely positive for mammoglobin and focally positive for S100. GATA3 was negative. Similar to secretory carcinoma of the salivary gland, primary secretory carcinoma of the thyroid is characterized by an ETS variant 6 (*ETV6*) and neurotrophic tyrosine kinase receptor type 3 (*NTRK3*) gene fusion.^{2,3} Fluorescence *in-situ* hybridization (FISH) for *ETV6* rearrangement was performed, and showed *ETV6* rearrangement in 80% of nuclei. The clinical history was reviewed to confirm that there was no history of salivary gland or breast carcinoma. Additionally, the patient had no history of radiation exposure. A diagnosis of primary secretory carcinoma of the thyroid with high-grade features was rendered.

Primary secretory carcinoma of the thyroid has been described only recently, with fewer than 10 cases reported in the literature.^{1-3,5,6} The tumour, as described in our case, is histologically similar to secretory carcinoma of the salivary gland (previously termed mammary analogue secretory carcinoma).⁷ The majority of reported cases of primary secretory carcinoma of the thyroid present at a high stage, and lymph node metastases, although absent in our case, are frequent.¹⁻³ Currently available clinical outcome data suggest that primary secretory carcinoma of the thyroid is associated with long-term survival, although one patient with a tumour without high-grade features died of disease 8.9 years after initial diagnosis due to widespread distant metastases.¹⁻³ Although the majority of secretory carcinomas of the salivary gland and thyroid are morphologically low grade, salivary gland secretory carcinoma with high-grade transformation has been reported,⁸ and there is one other reported case of primary secretory carcinoma of the thyroid with high-grade features (i.e. with necrosis and increased mitotic activity).¹ The prognosis of secretory carcinoma of the thyroid with high-grade features has not been established; however, all cases of salivary gland secretory carcinoma with high-grade transformation and the one case of primary thyroid secretory carcinoma with high-grade features pursued an aggressive clinical course, with all patients dying of disease.^{1,8} The cell of origin of secretory carcinoma of the thyroid has not been established, but in a series reported by Dogan and colleagues two cases were associated with conventional PTC (both components showed the

ETV6-NTRK3 fusion, but the PTC component was positive for TTF-1 and negative for mammaglobin, whereas the secretory carcinoma was negative for TTF-1 and positive for mammaglobin, indicating that follicular cells may be the cell of origin.² Our case had no associated PTC. Unlike the small subset of PTCs with *ETV6-NTRK3* fusion that are often associated with radiation exposure,⁹ the reported cases of primary thyroid secretory carcinoma thus far have not been associated with a history of radiation exposure.

The diagnosis of primary secretory carcinoma of the thyroid is challenging because of its morphological overlap with PTC. However, secretory carcinoma has distinct cytological and histological features. Cytologically, similar to PTC, secretory carcinoma demonstrates nuclear enlargement, clearing, contour irregularities, grooves and, in some cases, rare pseudoinclusions. The signet-ring-cell morphology differentiates secretory carcinoma from the vast majority of PTC. Signet-ring cells are a rare finding in thyroid FNAs. Although they are not entirely specific to secretory carcinoma (other diagnostic considerations include signet-ring cell follicular adenoma, parathyroid neoplasms, medullary thyroid carcinoma and metastatic signet-ring cell carcinoma), our case indicates that secretory carcinoma should be considered if signet-ring cells are seen on cytological evaluation. Additionally, the nucleoli of secretory carcinoma are larger, more eosinophilic and located centrally, in contrast to the dainty, dot-like, peripherally-located nuclei of PTC. Based on the prominent central nucleoli along with the nuclear contour irregularities, an oncocyctic (Hurthle cell) neoplasm may also be considered cytologically in the differential diagnosis. However, oncocyctic thyroid tumours have more granular cytoplasm compared to secretory carcinomas and lack the signet-ring cells. Additionally, oncocyctic thyroid tumours are characterized typically by discohesive single cells, whereas secretory carcinomas may show a more complex architecture, including the cribriforming that could be appreciated on the FNA of this case. The FNA findings of one other secretory carcinoma of the thyroid have been reported.⁶

Although there are many histological similarities between secretory carcinoma and PTC, several histological features are distinct. Even in Skalova's initial description of secretory carcinoma of the salivary gland, she noted histological similarity to thyroid, indicating that 'other diagnostic criteria include a microcystic honeycombed pattern composed of small cysts often merging into larger cysts with resemblance to thyroid follicles'.⁴ Moreover, the eosinophilic, intraluminal secretions of secretory carcinoma can easily be misinterpreted as colloid, and psammomatous calcifications have been reported in secretory carcinoma of the thyroid.³ In contrast to colloid, the secretory material is negative for thyroglobulin, but positive for periodic acid-Schiff (PAS) both with and without diastase and for mucicarmine. The growth pattern of secretory carcinoma is often heterogeneous. In addition to the cribriform and microcystic architecture that was prominent in our tumour, cases can have tubular, solid or trabecular growth and areas with papillary and micropapillary morphology. The cribriform and microcystic architecture of secretory carcinoma is striking, and usually not encountered in PTC. Cribriform morular variant of PTC is defined by its cribriform architecture; however, these tumours are characterized by a lack of associated colloid (the cribriform spaces are empty). In contrast, many of the cribriform spaces of secretory carcinoma contain the intraluminal eosinophilic secretory material. If a diagnosis of cribriform morular variant of PTC were considered, a β -catenin stain could be performed which would show aberrant nuclear and cytoplasmic localization in the case of cribriform

morular variant of PTC. Additionally, the intracytoplasmic vacuoles with eosinophilic material seen in secretory carcinoma are not seen in PTC.

In our case the tumour was diagnosed initially as poorly differentiated thyroid carcinoma. The Turin proposal defines PDTC as a tumour with a solid/insular/trabecular architecture that lacks nuclear features of PTC and additionally shows convoluted nuclei, 3 mitoses per 10 HPFs or tumour necrosis.¹⁰ This tumour lacked the solid/trabecular/insular growth of poorly differentiated thyroid carcinoma. In addition, the nuclei were enlarged and clear, unlike the smaller darker nuclei of poorly differentiated thyroid carcinoma. Hiltzik and colleagues showed that thyroid tumours, regardless of growth pattern, with a mitotic count of five or more per 10 HPFs and/or tumour necrosis, pursue a clinical course similar to that of poorly differentiated thyroid carcinoma defined by Turin criteria (many endocrine pathologists term PTCs that fulfill the Hiltzig criteria but not the Turin criteria as PTC with high-grade features).¹¹ Thus, our tumour could be misinterpreted as a PTC with high-grade features. However, recognizing secretory carcinoma as a distinct thyroid tumour is important for several reasons. First, even without high-grade features, secretory carcinoma appears prone to multiple recurrences and thus demonstrates a more aggressive clinical course than the majority of PTCs.^{1–3} Moreover, disease status can not be monitored with thyroglobulin levels, and secretory carcinoma would not be expected to respond to radioactive iodine. Differentiating secretory carcinoma from PTC with high-grade features is important, because targeted treatment based on the presence of the underlying *ETV6-NTRK3* fusion could be considered for patients with secretory carcinoma that pursue an aggressive clinical course. Recently, the pan-Trk inhibitor entrectinib was shown to be efficacious in the treatment of a widely metastatic salivary gland secretory carcinoma.¹²

In addition to the cytological and histological features that distinguish secretory carcinoma from PTC, immunohistochemistry and cytogenetics are important to confirm the morphological impression. Secretory carcinoma and PTC (with or without high-grade features) are both positive for PAX8, although the expression is weak to moderate in secretory carcinoma and a PAX8-negative primary secretory carcinoma of the thyroid has been reported.¹ The PAX8 positivity of secretory carcinoma of the thyroid may support that this tumour is thyroid in origin or may be non-specific. In contrast to PTC (with or without high-grade features), secretory carcinoma lacks expression of TTF-1 and thyroglobulin. Secretory carcinoma is positive for mammoglobin and S100. Additionally, although negative in our case, GATA3 can be positive in secretory carcinoma of the thyroid,^{1,3} and the tumour is also positive for gross cystic disease fluid protein (GCDFP) and can be focally positive for p63.^{1,2} FISH or molecular analysis can be performed to assess for an *ETV6* rearrangement. Both secretory carcinoma of the thyroid and of the salivary gland harbour an *ETV6-NTK3* fusion. This fusion is also found in secretory carcinoma of the breast, infantile fibrosarcoma, congenital mesoblastic nephroma and subsets of PTCs, haematopoietic malignancies and ALK-negative inflammatory myofibroblastic tumours.¹³ The fusion results in a constitutively active protein tyrosine kinase and downstream activation of the Ras-mitogen-activated kinase (MAPK) and phosphatidylinositol-3-kinase–protein kinase B (Akt) pathways. Approximately 15% of radiation-associated PTCs and 2% of sporadic PTCs have been found to harbour an *ETV6-NTK3* fusion.⁹ Recently, the *NTRK* fusion oncogenes (including *ETV6-NTRK3*) have been reported in a quarter of paediatric PTCs, suggesting

that these fusions may be more common in PTCs in children.¹⁴ PTCs with the *ETV6-NTRK3* fusion have been reported to be classical type and follicular variant, with many tumours including a solid component and some of the follicular variants demonstrating a diffuse growth pattern.^{9,14} Secretory carcinoma of the salivary gland and radiation-associated PTC typically demonstrate different *ETV6-NTRK3* fusion breakpoints.^{4,9} Typically, salivary gland secretory carcinoma is associated with the fusion of exon 5 of *ETV6* with exon 15 of *NTRK3* and radiation-associated PTC exhibits fusion of exon 4 of *ETV6* with exon 14 of *NTRK3* (although fusion of exon 4 of *ETV6* with exon 14 of *NTRK3* has been reported in salivary gland secretory carcinoma).^{4,9,13} In the few cases of secretory carcinoma of the thyroid in which the fusion breakpoints have been evaluated, the fusion has involved exon 4 of *ETV6* and exon 14 of *NTRK3*.^{2,3} Thus, these findings indicate that even in the presence of an *ETV6-NTRK3* fusion, other morphological features to differentiate PTC from secretory carcinoma must be considered; moreover, the clinical history must be reviewed to ensure that the patient does not have a salivary gland or breast primary.

In summary, we describe a case of primary secretory carcinoma of the thyroid with increased proliferative activity and tumour necrosis. Differentiating secretory carcinoma from PTC is crucial both for prognostication and treatment purposes. Our patient is currently being treated with concurrent chemotherapy (taxol and carboplatin) and external beam radiation; however, therapy with a pan-Trk inhibitor could be considered in the future depending on the clinical course of disease.

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Figure 1. Computed tomography (CT) of the neck soft tissue (with contrast). On imaging, there is asymmetric enlargement of the thyroid gland with secondary minimal displacement of the trachea to the right. The tumour is isodense (post-contrast) to the surrounding soft tissues, and abuts but does not invade the trachea.

Figure 2.

Cytological features of secretory carcinoma of the thyroid. **A**, The cells had a moderate amount of cytoplasm and nuclei with vesicular chromatin, prominent centrally-located nucleoli and some nuclear contour irregularities and grooves. The signet-ring-cell morphology of some of the cells was striking in this case, and should raise the possibility of secretory carcinoma. **B**, A cribriform architecture was apparent on the cell block with luminal colloid-like secretory material.

Figure 3.

Histological features of secretory carcinoma of the thyroid. **A**, The tumour was infiltrative and associated with abundant hyalinized stroma. **B**, The tumour had a predominantly cribriform architecture. **C**, Focally the tumour showed papillary and micropapillary growth with adjacent multilayered epithelium. **D**, The tumour cells were uniform with enlarged nuclei with prominent centrally-located nucleoli. The intracytoplasmic vacuoles with eosinophilic secretory material correlate with the signet-ring cells seen on fine-needle aspiration (FNA). **E**, Mitoses were readily identified (numbering up to seven per 10 high-power fields (HPFs)). **F**, Tumour necrosis was present.