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ORIGINAL PAPER

Secretory Carcinoma of the Thyroid Gland: Report of a Highly Aggressive Case Clinically Mimicking Undifferentiated Carcinoma and Review of the Literature

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Abstract
After being described in the salivary glands as a malignancy with features essentially identical to those of the breast, secretory carcinoma (SC) (formerly mammary analogue SC) has now been identified in other sites including the skin, lung, and thyroid gland. In the breast, SC has a relatively favorable prognosis. Likewise when arising in the salivary glands, it is generally considered to be a low to intermediate grade carcinoma; however, there is a range of clinical behavior with occasional patients dying of progressive disease. SCs of the thyroid gland are rare, and reports suggest a relatively aggressive behavior, at least relative to well differentiated carcinomas such as papillary carcinoma and minimally invasive follicular carcinoma. We present a patient with a highly aggressive thyroid gland SC that mimicked undifferentiated carcinoma clinically. The patient had widespread metastatic disease and died rapidly from airway compromise. We also review the literature for reported cases of thyroid gland SC in order to better establish the clinical features and expected clinical course of such tumors occurring at this site.

Keywords Mammary analogue secretory carcinoma · Thyroid · ETV6 gene rearrangement · Papillary carcinoma · Anaplastic carcinoma

Introduction

Secretory carcinoma (SC) is an exceedingly rare invasive carcinoma of the breast that occurs in young patients (median age 25 years), has a favorable prognosis, exhibits a unique histomorphology, and harbors a characteristic recurrent balanced chromosomal translocation t(12;15)(p13;q25) resulting in *ETV6-NTRK3* gene fusion product. These tumors are composed of uniform, bland epithelial cells arranged in solid, microcystic, and tubular patterns with abundant granular, eosinophilic extracellular and intracellular secretions [1–4]. Skalova et al. first described a morphologically and genetically identical tumor arising in the salivary glands in 2010 and so termed it "mammary analogue secretory carcinoma" (MASC) [5]. The latest (2017) World Health Organization (WHO) classification of head and neck tumors categorizes this new entity simply as "secretory carcinoma" [6, 7]. SC of the salivary gland is generally considered an indolent tumor with a favorable prognosis and prolonged disease-free survival interval, similar to acinic cell carcinoma (AciCC), (92 and 121 months, respectively) [8]. However, occasional patients have had an aggressive clinical course, and a few patients have shown histologic progression to a much higher grade tumor (so-called "high grade transformation") [9]. The original cases were primarily identified in the parotid gland with a subset arising in minor salivary glands [5]. SC has since been identified in other sites, such as the skin, lung, and sinonasal mucosa [10–15]. In August 2015, the first case of SC arising in the thyroid

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gland was described and subsequently nine more cases have been reported [16–20]. These tumors have variable clinical behavior, but overall seem to be more aggressive than SC of the breast or salivary gland and well differentiated thyroid carcinomas such as papillary and follicular. We report the tenth case in the literature of SC, this one clinically mimicking undifferentiated/anaplastic carcinoma, review the current literature on non-mammary, non-salivary SC, and discuss their clinical behavior and management.

Case Report

A 74 year old woman presented to her local emergency room with shortness of breath and marked stridor. She required intubation shortly thereafter for hypoxic respiratory failure. The patient's husband reported that the patient had a 3 month history of cough and progressive dyspnea with rapidly increasing neck swelling over the preceding 2 weeks. Her medical history was notable for hypertension, osteoarthritis, and a remote cholecystectomy. She was a non-smoker and non-drinker and had no history of cancer. Her family history, though, was remarkable for siblings with lung cancer and breast cancer. Physical examination revealed swelling of the anterior neck extending to the upper chest and palpable bilateral cervical lymphadenopathy. Laboratory studies were notable only for a mildly elevated white blood cell count. Thyroid function tests and calcium levels were within normal limits.

The patient was transferred to a tertiary care center where computed tomography imaging (Fig. 1) revealed massive thyromegaly extending into the mediastinum and causing compression of the large vessels and subglottic airway to the level of the carina. Several areas of hypoattenuation within the mass were thought to represent tumor necrosis. There were also masses within the lung, liver (measuring up to 4.4 cm) and kidney, an iliac bone lesion, and necrotic cervical, supraclavicular, and mediastinal lymph nodes suspicious for metastatic disease.

Fine needle aspiration (FNA) of the right thyroid lobe showed a cellular specimen composed of loosely cohesive sheets and clusters of monomorphic cells forming vaguely acinar structures. The nuclei were uniformly enlarged with rare nuclear contour irregularities, dispersed chromatin, occasional grooves and variably prominent, centrally placed nucleoli. The cytoplasm was abundant, eosinophilic, and fluffy (Fig. 2). These findings were concerning for papillary thyroid carcinoma (PTC). However, immunohistochemical stains for thyroid transcription factor 1 (TTF-1) and thyroglobulin (TG) on limited cell block material were indeterminate due to low cell volume. She suffered two hypoxic pulseless electrical activity cardiac arrests while intubated due to the severity of airway obstruction. The size of the tumor prevented tracheotomy, and therefore the patient was taken to the operating room for a debulking procedure. Intraoperatively, a dense tumor was noted to completely infiltrate the thyroid gland and extend into the mediastinum and paratracheal space bilaterally with severe compression of the trachea. A frozen section of thyroid isthmus was reported as "adenocarcinoma". The trachea was surgically decompressed with an extensive right hemithyroidectomy, neck, and mediastinal dissection. The patient was unfortunately extubated for only a brief time following this surgical procedure before requiring re-intubation for respiratory distress. She was then taken back to the operating room on postoperative day three for further debulking via left hemithyroidectomy and tracheotomy.

The right and left hemithyroidectomy specimens were markedly enlarged, weighing 199 g in aggregate. Gross examination showed scant residual normal thyroid

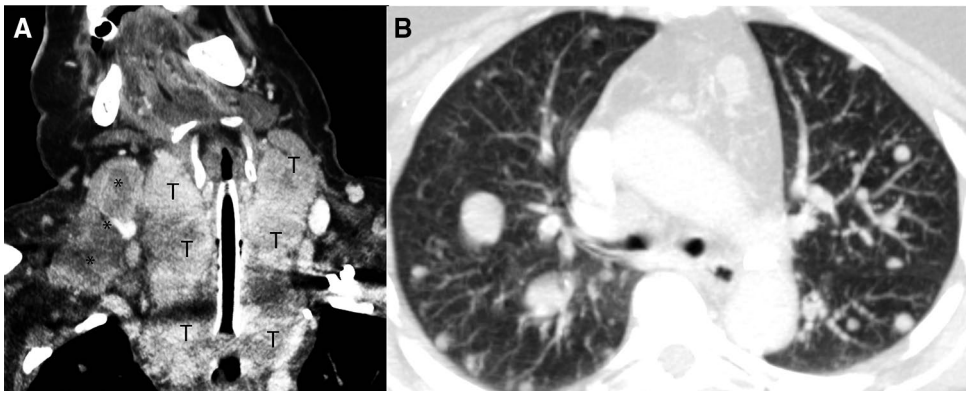

Fig. 1 **a** Coronal post-contrast computed tomography neck image through the trachea (endotracheal tube in place) showing massive bilateral enlargement of the thyroid gland (T), extending inferiorly to the aortic arch and superiorly to the top of the thyroid cartilage. Bulky right middle and inferior lateral neck adenopathy (*). **b** Axial computed tomography chest maximum intensity projection image (15 mm thickness) showing multiple, bilateral, rounded lung metastases

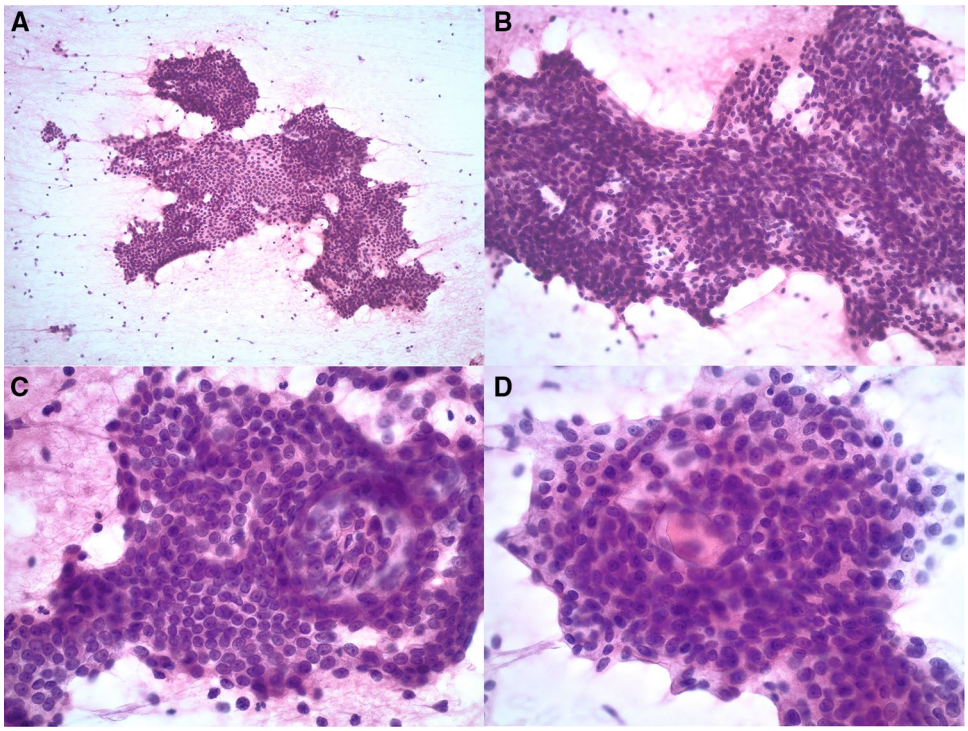

Fig. 2 **a, b** Fine needle aspiration smear is hypercellular with cohesive sheets and clusters of monomorphic cells with vaguely acinar and pseudopapillary structures ('tentacular nubbins'). **c, d** The tumor cells show dispersed chromatin with variably prominent, centrally-placed nucleoli, occasional grooves, and abundant, vacuolated, eosinophilic cytoplasm. Eosinophilic colloid-like secretions are present

parenchyma with diffuse replacement by multiple masses, the largest measuring 7.6 × 5.3 × 2.7 cm, with infiltrative borders and extension into surrounding adipose tissue. The cut surfaces were white-tan, variegated, focally hemorrhagic and occasionally bulging. Large amounts of necrosis were present. Multiple paratracheal, cervical, and mediastinal lymph nodes were firm, white-tan and grossly suspicious for metastatic disease.

Histologic examination of the right thyroid lobe (Fig. 3) revealed diffuse involvement by neoplastic cells arranged in variably sized lobules separated by collagenous stroma. Within these lobules, cells were arranged in a variety of architectural configurations, predominantly solid and follicular with foci of microcystic, cribriform, and papillary/micropapillary (approximately 10%) patterns. Abundant intraluminal collections of dense, eosinophilic, colloid-like secretions with occasional vacuolization were present. In some areas, these secretions were lightly eosinophilic and in others more basophilic. The neoplastic cells had enlarged oval to round nuclei with vesicular chromatin, small nucleoli, and ample, finely granular, eosinophilic cytoplasm. The nuclei had irregular contours but few grooves and no intra-nuclear cytoplasmic inclusions. Despite the prominent necrosis, mitotic activity was low (two per ten high power fields). All margins were involved, and there were multiple foci of extrathyroidal extension.

Immunohistochemistry for PAX8 and TG were focally and weakly positive and TTF-1 was negative. On the basis of these findings, a diagnosis of PTC, classical type, was made. Histologic examination of the completion left hemithyroidectomy specimen (Fig. 3) was similar with multifocal tumor in mixed architectural patterns including papillary, follicular, and solid. There were again abundant intraluminal collections of lightly eosinophilic, and in other areas, basophilic, vacuolated material with irregular borders. Tumor cells were uniform with round to oval nuclei with eosinophilic, finely granular cytoplasm. The diagnosis was further considered and additional immunohistochemical stains for GATA3 and S100 were performed. These were both strongly positive in the neoplastic cells. A PAX8 stain was focally and weakly positive and TTF-1 and TG stains were negative. Re-review of the initial hemithyroidectomy specimen combined with the additional immunohistochemistry results showing strong positivity for GATA3 and S100 led to the diagnosis of "mammary analogue secretory carcinoma" (SC) and correction of the diagnosis on the first thyroidectomy specimen [6, 7]. On the additional specimens, tumor was again present at all peripheral resection margins with extensive extrathyroidal extension. Five of five examined regional lymph nodes showed metastatic carcinoma with extranodal extension. The overall pathologic TNM staging for this patient was T4aN1aM1. Subsequent research-based fluorescent in situ hybridization (FISH) using a commercially available ETV6 dual color break apart probe (07j77-001, Abbott Molecular, Des Plaines, IL) confirmed translocation of the *ETV6* gene in 100% of tumor nuclei (Fig. 4). Overall, the tumor had been well sampled, with one section examined per 0.7 cm of tumor across both specimens.

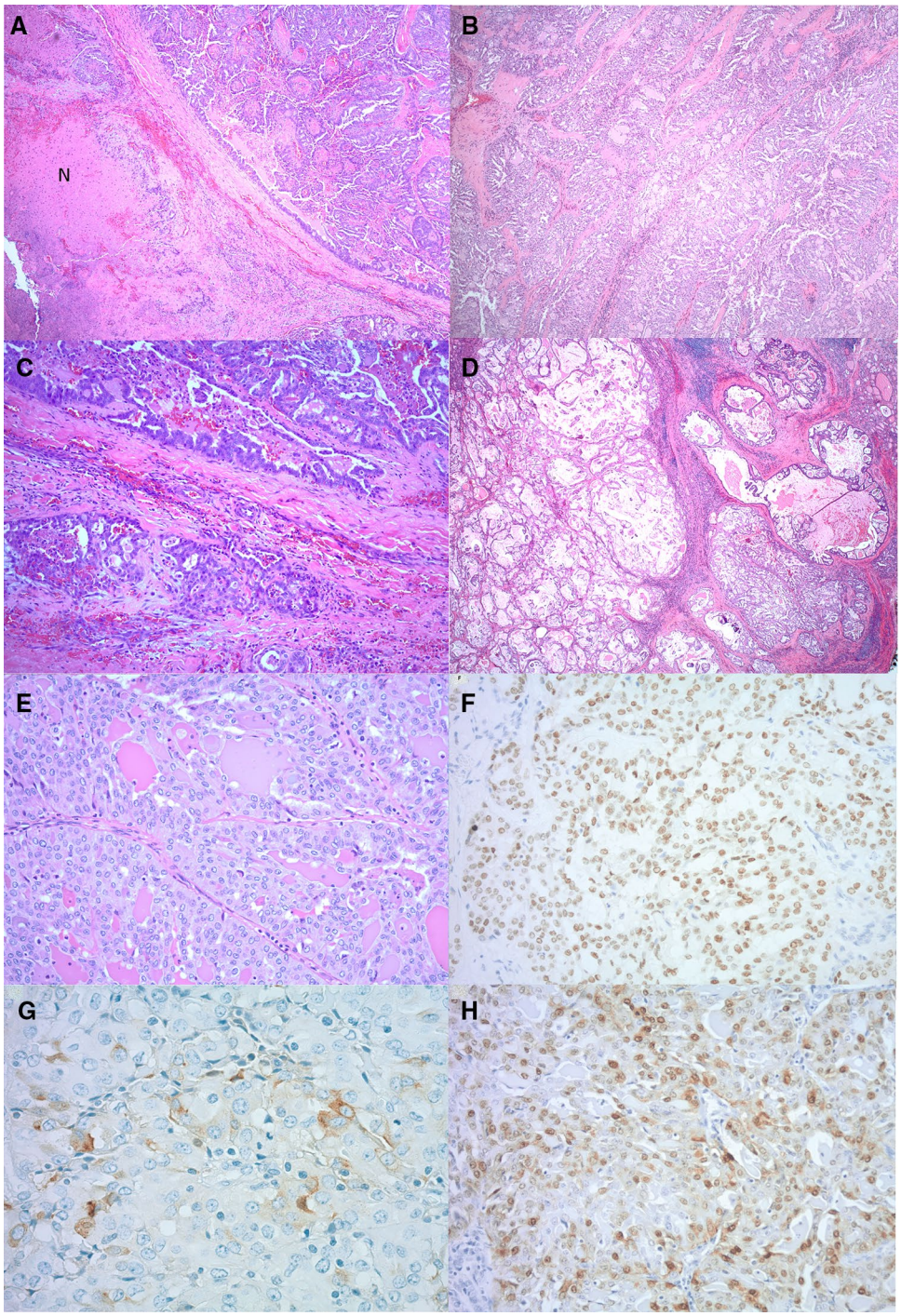

Fig. 3 **a**–**d** Hematoxylin and eosin-stained sections of the thyroidectomy specimen demonstrating lobules of tumor separated by hyalinized stroma, composed of cells arranged in various architectural patterns ranging from solid to trabecular to micropapillary to cribriform. Large areas of necrosis are present (indicated by N). Intraluminal eosinophilic secretions are present with peripheral vacuolization. The tumor cells have large, round to ovoid nuclei with vesicular chromatin, central nucleoli, and abundant granular, eosinophilic cytoplasm. **e** The secretions are positive on periodic acid Schiff (PAS) staining. **f** Immunohistochemistry for GATA-3 showed strong diffuse nuclear staining. **g** Immunohistochemistry for GCDFP-15 showed patchy positive cytoplasmic staining. **h** Immunohistochemistry for S-100 showed extensive, but moderate intensity, nuclear and cytoplasmic staining

The patient was not a candidate for systemic chemotherapy or radiation given her clinical condition. She was transitioned to palliative care and died 22 h later. A post-mortem examination limited to sampling of areas of suspected metastatic disease showed bulky tumors throughout the right and left lungs, liver, and right and left kidneys. The lesions were firm with white-tan cut surfaces and focal hemorrhage, cystic change, and abundant necrosis. Histologic examination revealed similar features to the original tumor with neoplastic cells arranged in a variety of growth patterns from solid nests with microcystic, cribriform, and micropapillary areas (Fig. 3). While the course was aggressive clinically, the carcinoma had similar histologic features at all sites, without evidence of de-differentiation (or so-called high grade transformation).

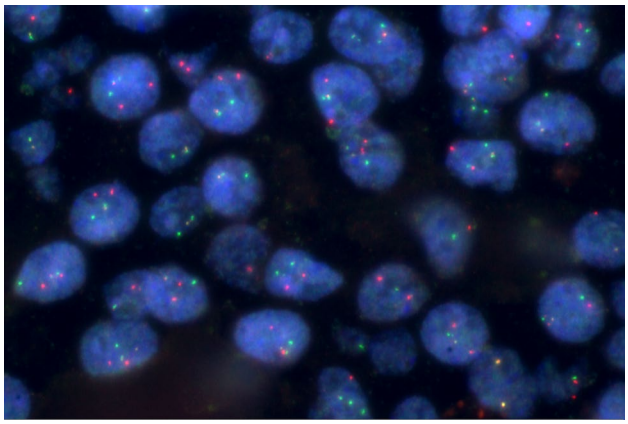

Fig. 4 Fluorescence in situ hybridization using ETV6 dual color, break apart rearrangement probes demonstrates *ETV6* rearrangement in 100% of tumor cells. 22% of cells have the typical pattern of one intact gene (red and green signals together) and one rearranged gene (separate red and green signals). 78% of cells have a unique pattern of one intact gene and one rearranged gene with two red signals (ie; gain of red signal)

Discussion

Salivary gland SC is a recently described and relatively rare neoplasm, so named because of its histologic resemblance and genetic similarity to SC of the breast, which generally occurs in young patients and has a favorable prognosis [4]. These tumors are defined by the presence of a recurrent balanced translocation t(12:15) resulting in fusion of the *ETV6* gene. Skalova et al. first described SC arising in the salivary gland in 2010 upon retrospective review of 16 salivary gland tumors previously classified as AciCC, adenoid cystic carcinoma, cystadenocarcinoma, or low-grade carcinoma not otherwise specific [5]. The tumors in these cases morphologically resembled breast SC with mixed microcystic, tubular, and solid growth patterns, low-grade, vesicular nuclei, and pale eosinophilic, granular to vacuolated cytoplasm and were uniformly positive for S100, vimentin, and mammaglobin. FISH confirmed t(12;15)(p13,q25) translocation in each of the 11 analyzable cases, with *ETV6-NTRK3* fusion transcripts detected by RT-PCR in 13 of 14 cases. Given the morphologic and molecular genetic similarities, these tumors were thus termed MASC. The 2017 WHO classification of head and neck tumors formally designates this new entity simply as "secretory carcinoma" (SC) [6, 7]. Since 2010, many groups have re-analyzed their historic salivary gland tumor cases and found that up to 11% of cases previously diagnosed as AciCC are in fact SC [21]. More than 150 cases have now been reported in the literature, and SC appears to actually represent approximately 3–4% of primary salivary gland tumors [22].

SC of the breast has a well-documented favorable prognosis with a 5-year and 10-year disease specific survival of 94.4% and 91.4%, respectively [4, 23]. SC of the salivary gland is similarly considered an indolent tumor with a favorable prognosis and prolonged disease-free survival interval similar to AciCC (92 and 121 months, respectively) [8]. As such, current literature suggests SC of salivary gland can be managed similarly to AciCC and other low grade salivary gland carcinomas with surgical resection and, when indicated for other adverse features, local radiation.

Since Skalova's first description in 2010 of extra-mammary SC in salivary glands, SC has been reported in multiple extra-salivary locations including thyroid gland and skin. No ectopic breast or salivary tissue has been definitively identified in these anatomic locations or within/around the tumors. These tumors demonstrate morphologic and immunohistochemical similarities to SC of the breast and salivary glands and have identical genetic rearrangements of *ETV6* [16–20, 24, 25]. A total of ten cases of SC in the thyroid have previously been reported in the literature [16–20, 26, 27]. Here we report the eleventh.

The clinical characteristics of all published cases of thyroid SC are presented in Table 1. The average age of presentation (59 years, range 36–74 years) is similar to, but slightly older than, that of SC of salivary glands where the average age is 44–46 years [28, 29]. There is a strong female predominance (9/11, 81.8%) for thyroid SC in contrast to the near equal to slight male predominance seen in SC of salivary gland [18, 28, 29]. This may be due to the small number of reported cases and might not necessarily persist in larger cohorts. It would, however, fit with thyroid carcinoma in general, where there is an overall female predominance. No patients had prior radiation exposure. Radiologic findings have not been reported in every case, but in our case and the case reported by Reynolds et al., the thyroid was massively enlarged and heterogeneous with significant compression of adjacent organs [17]. Results of radioactive iodine uptake studies have not been previously reported and were not performed in our case. Similarly, results of laboratory studies are scarce. TG levels were undetectable to low in the two cases where it was reported. Thyroid stimulating hormone level was normal (0.635 μU/ml, ref range 0.35–3.6) in our case while elevated (88.05 μU/ml) in one case reported by Dogan et al. [30].

Grossly the tumor masses in the ten cases of thyroid SC have been quite large, ranging from 2.4 to 7.6 cm, infiltrative, poorly circumscribed, solid, and white-grey to tan-yellow in color. Affected patients tend to present with high T stage (6/11 with T4, 3/11 with T3) and locally advanced disease. On post-mortem examination, our patient's tumor grossly encased large mediastinal vessels (T4b). Most cases (6/10) had lymph node involvement at the time of diagnosis with frequent extranodal extension. Our case represents the first patient in the literature with distant metastasis at diagnosis.

Table 1 Clinical features of all reported cases

Case	Age (years)	Sex	Size (cm)	Stage	Distant metastases?	Margins	Treatment (in addition to surgical resection)	Follow up (mos)	Outcome
Stevens/Dettloff	55	F	2.6	T4aN1a	N	NR	XRT	43	NED
Reynolds/Rupp	36	F	4.5	T4aN1	Y, at recurrence (soft tissue + lung + liver)	Pos	RAI kinase inhibitor + XRT	105	Recurrence x2, DoD
Dogan	72	F	2.9	T4aN0	N	Focal pos	RAI	204	Recurrence x2, NED
	47	M	7.0	T3N1b	N	Neg	RAI NTRK3 inhibitor trial	168	Recurrence x3, AWD
	65	F	6.5	T4aN0	N	Pos	RAI XRT	24	NED
Dettloff	52	F	2.4	T2N1a	N	NR	None	26	NED
	74	M	4.0	T2N1b	Y, at recurrence (liver)	NR	Chemo XRT	12	DoD
Wu	58	F	4.0	T4aN0	N	Pos	Taxol + carboplatin XRT	NR	Alive
Liao	58	F	4.0	T4aN0	NR	Pos	Taxol + carboplatin XRT	14	NED
Asa	72	F	2.5	T3N0	N	NR	NR	18	NED
Current case	74	F	7.6	T4bN1b	Y, at diagnosis (liver, lung, kidney)	Pos	None	20 days	DoD

AWD alive with disease, *DoD* died of disease, *N* no, *NED* alive with no evidence of disease, *neg* negative, *NR* not reported, *pos* positive, *RAI* radioactive iodine, *XRT* radiation therapy, *Y* yes

The histopathologic features of SC of the thyroid are presented in Table 2 and are similar to those seen in the salivary gland [29]. They include architecturally variability with a range of growth patterns (microcystic, cribriform, solid, trabecular, and papillary or pseudopapillary), densely hyalinized and fibrotic stroma and eosinophilic to lightly basophilic intraluminal secretions, occasionally with peripheral spaces/scalloping. The comprising tumor cells are polygonal and generally uniform with low to medium nuclear-to-cytoplasmic ratio. Cytoplasm is abundant and eosinophilic and ranges from granular to bubbly or vacuolated with intracytoplasmic eosinophilic secretions. Nuclei are round to ovoid with vesicular chromatin. Nuclear grooves and membrane irregularities may be prominent. Pseudoinclusions are rare, but may be seen. Nucleoli are generally single, prominent and centrally located and may be eosinophilic. The combination of some papillary growth and the nuclear features strongly suggests PTC, but the other histologic features and the immunohistochemical findings are incongruent with PTC. PTC is a well differentiated carcinoma with follicular differentiation, so negative TTF-1 and/or TG immunostains should prompt consideration of an alternative diagnosis.

Rupp and Bocklage recently provided the first comprehensive cytopathologic description of SC of thyroid [20]. They reported a hypercellular aspirate of variable architecture including sheets, fragmented pseudopapillae and 'tentacular nubbins' ("three dimensional, complex, branching aggregates featuring short, broad, protruding pseudopapillae"). The tumor cells possessed abundant, granular cytoplasm with prominent vacuolization. Nuclei were enlarged and vesicular with prominent grooves and single, centrally placed nucleoli and rare pseudoinclusions. Wu et al. have recently corroborated this cytopathologic description [26]. In their case, the aspirate was cellular and comprised of sheets of tumor cells with moderate cytoplasm, vesicular nuclei and single, centrally prominent nucleoli. Intracytoplasmic vacuoles resulted in "signet ring cell" morphology. The cell block demonstrated a cribriform architecture with luminal secretions. In our case, the aspirate was similarly cellular with cohesive groups of cells arranged in sheets and pseudopapillae with 'tentacular nubbins' evident. Nuclei were enlarged with occasional grooves (Fig. 2).

As noted in Table 2, all reported cases of SC of the thyroid have been negative for TTF-1 and TG while positive for mammaglobin and S100 (one exception, case 10), though staining may be patchy and of variable intensity. Mammaglobin IHC was not performed in our case although tumor cells in our case were positive for GCDFP-15 (Fig. 3). PAX8 immunoreactivity has been noted in 9/10 (90%) reported cases and is frequently focal and weak, as in our case. Tumor cells in five of six (83%) cases, including our case, demonstrated focal GATA3 expression (Fig. 3). Intraluminal

Table 2 Histopathologic features of all reported cases

Case	Histomorphology		Background thyroid	Necrosis?	Associated PTC?	Immunohistochemistry								ETV rearrangement? (method)
	Architecture	Cytology				TTF1	TG	PAX8	S100	MG	GCDFP15	GATA3	Ki67	
Stevens/Dettloff	Cribriform with dense eos mucin	Polygonal, eos vacuolated cytoplasm, low grade, low mitotic rate, small to medium-sized nuclei, occ. nucleoli, nuclear grooves and overlap, abundant pink/bubbly cytoplasm, no zymogen granules	NR	N	N	Neg	Neg	Pos	Pos	Pos	NR	Pos	NR	Y (FISH)
Reynolds/Rupp	Multinodular, fibrous stroma, variable (follicular, papillary, microcystic, trabecular), intra- and extra-cellular eos globules, follicle-like spaces with peripheral clear bubbles	Round to columnar epithelial cells, granular and variably eos cytoplasm, oval and vesicular nuclei, prominent central nucleoli, numerous nuclear grooves, psammomatous calcifications	Lymphocytic thyroiditis	N	NR	Neg	Neg	NR	Patchy	Pos	NR	Patchy	NR	Y (FISH, PCR)
Dogan	Lobules, nests, and cords, separated by dense collagenous stroma, variable patterns (cribriform, papillary, pseudopapillary, microcystic)	Evenly spaced, dense eos vacuolated cytoplasm, smooth nuclear contours, open to finely coarse chromatin, prominent nucleoli, low mitotic rate	Lymphocytic thyroiditis	NR	N	Neg	Neg	Weak	Rare	Pos	Focal	NR	1–2%	Y (FISH, 65% nuclei)
			Lymphocytic thyroiditis	NR	Y	Neg	Neg	Weak	Rare	Pos	Neg	NR	< 1%	Y (FISH, 83% nuclei)
			Lymphocytic thyroiditis	NR	Y	Neg	Neg	Weak	Pos	Pos	Focal	NR	5%	Y (FISH, 83% nuclei)

Table 2 (continued)

Case	Histomorphology		Background thyroid	Necrosis?	Associated PTC?	Immunohistochemistry								ETV rearrangement? (method)
	Architecture	Cytology				TTF1	TG	PAX8	S100	MG	GCDFP15	GATA3	Ki67	
Dettloff	Encapsulated, hyalinized, variable pattern (papillary, cribriform with pale pink to eos mucin)	Polygonal, eos vacuolated cytoplasm, low mitotic rate, round nuclei with nuclear clearing, small nucleoli, nuclear grooves	NR	N	N	Neg	Neg	Neg	Pos	Pos	NR	NR	NR	Y (FISH)
	Glandular admixed with focal papillary, dense eos to purple mucin	Polygonal, eos vacuolated cytoplasm, high mitotic rate, open chromatin, red nucleoli, nuclear grooves	NR	Y	N	Neg	Neg	Focal	Pos	Pos	NR	Focal	NR	Y (FISH)
Wu	Hyalinized stroma, cribriform and microcystic with colloid-like material with focal papillary and micropapillary growth	Uniform, moderate eos cytoplasm with frequent vacuoles with eos material, enlarged nuclei, vesicular chromatin, prominent eos and centrally placed nucleoli, nuclear contour irregularities, nuclear grooves, frequent mitotic figures	Lymphocytic thyroiditis	Y	NR	Neg	Neg	Pos	Focal	Pos	NR	Neg	20%	Y (FISH, 80% nuclei)
Liao	Dense fibrotic stroma, solid, nested, microcystic, and focal papillary, intraluminal and eos secretions	Abundant eos cytoplasm, prominent nucleoli, foci of enlarged cells with irregular nuclear grooves	NR	Y	NR	Neg	Neg	Pos	Rare	Pos	Pos	Rare	NR	Y (FISH, 80% nuclei)

Table 2 (continued)

Case	Histomorphology		Background thyroid	Necrosis?	Associated PTC?	Immunohistochemistry							ETV rearrangement? (method)
	Architecture	Cytology				TTF1	TG	PAX8	S100	MG	GCDFP15	GATA3	Ki67	
Asa	Solid, follicular, cribriform, pseudopapillary, focal papillary, fibrotic stroma,	Abundant eos cystoplasm, round nuclei prominent nucleoli	Lymphocytic thyroiditis	N	Y	Focal	Neg	Weak	Neg	Nr	NR	NR	NR	NR
Current case			Nodular hyperplasia	Y	N	Neg	Neg	Weak	Pos	Nr	Patchy	Pos	NR	Y (FISH)

Eos eosinophlic, *LG* low grade, *N* no, *neg* negative, *NR* not reported, *pos* positive, *PTC* papillary thyroid carcinoma, *Y* yes, *TG* thyroglobulin, *MG* mammaglobin

secretions were positive for periodic-acid Schiff (with and without diastase) and for mucicarmine.

Frequent mitotic activity and necrosis were present in two published cases. Simpson et al. recently presented a third case with high grade features including abundant necrosis in an 84 year old female [31]. In two of these cases with high grade transformation, the patient died of disease and associated metastases within a short time (2–12 months). The third patient is alive and receiving treatment, but disease status is not known. The remainder of reported patients have no evidence of disease ($n=6$) or are alive with disease ($n=2$) at a relatively long average follow up interval (78 months, range 14–204 months). Local recurrence has been documented in two cases. Distant metastasis occurred remote from diagnosis in two patients, both of whom died of disease. These findings suggest that SC of the thyroid exhibits a spectrum of behavior, but overall a more aggressive clinical course, than for SC arising at any of the other reported primary sites.

SC of the breast and salivary gland are considered to have a moderate risk of local recurrence and lymph node metastases (approximately 35% and 15–20%, respectively) and a low risk of distant metastases [8, 32]. Patients with SC of the breast have a 5 year overall survival of nearly 96% [23]. Disease-free survival intervals for patients with SC of salivary gland (92 months) did not differ significantly from those with low grade AciCC (121 months) [8]. However, three cases of "high grade transformation" of SC of salivary gland, characterized by increased mitotic activity, comedo necrosis, desmoplastic stroma, and anaplasia, have been reported. All three of these patients died of disseminated disease within 24–72 months [9]. So called "high grade transformation" also has been reported in thyroid SC, but it is not clear if this represents transformation of a lower grade carcinoma to one that is poorly differentiated and much more clinically aggressive or just a spectrum of tumor biology. Interestingly, although necrosis was present in our case, there were no other histologic features of high grade transformation, and the tumor maintained a low mitotic rate (two per ten high power fields). And still, the patient presented similarly to undifferentiated thyroid carcinoma and died of rapidly progressive disease only 20 days after diagnosis.

SC of the salivary gland was originally defined by the t(12;15)(p13;q25) chromosomal rearrangement and resulting *ETV6-NTRK3* gene product identical to that found in SC of the breast [5]. This balanced translocation and fusion gene have also been described in congenital fibrosarcoma, the cellular variant of congenital mesoblastic nephroma, and rare cases of acute myeloid leukemia [33–37]. Our case and all of the nine other cases of SC of thyroid reported to date that were tested have all harbored the characteristic translocation (Table 2). Rearrangements involving *ETV6* and non-*NTRK3* partners have since been reported in SC of the salivary gland [38, 39]. To date, no alternate *ETV6* gene partners have been

reported in SC of the thyroid, although such cases should be anticipated.

As in at least six previously reported cases, our case was initially mistaken for PTC or poorly differentiated thyroid carcinoma. Occasional nuclear grooves, rare nuclear pseudoinclusions, colloid-like material, psammomatous calcifications, and frequent papillary architecture make this an understandable misdiagnosis both cytologically and histologically. Review of reported cases of SC of the thyroid shows that this tumor can be distinguished cytologically from PTC by signet ring cell morphology and 'tentacular nubbins' with pseudopapillae [20, 26]. Histologically, SC can be distinguished from PTC by the following features: cribriform and microcystic architecture with associated secretions, frequent small intracytoplasmic eosinophilic secretions, and a single and centrally located, prominent nucleolus. Further, the secretions are irregular and fluffy, with vacuolization and, unlike colloid, which is more dense and eosinophilic, vary in shape and color from lightly eosinophilic to basophilic. If suspected cytologically or morphologically, immunohistochemical stains can be used to easily distinguish SC from PTC as the two have essentially inverse staining patterns. SC is positive for mammaglobin and S100 while negative for TTF-1 and TG. Furthermore, eosinophilic secretions in SC will be positive for mucicarmine and PAS. Finally, FISH using break-apart probe for *ETV6* or PCR with *ETV6* and *NTRK3* can be used to confirm morphologic suspicion. It is important to recognize, however, that *ETV6-NTRK3* translocated PTC has been reported, in both radiation- and non-radiation-associated cases alike [37, 40–42]. Thus, the morphology and immunohistochemical features are key to distinguishing one tumor type from the other.

It is imperative to correctly diagnosis SC of the thyroid gland. Adjuvant therapy with radioactive iodine would not be expected to be effective since the tumors do not have follicular differentiation, as evidenced by lack of TG and TTF-1 expression. To date, all cases of thyroid SC have been treated with thyroidectomy followed by differing regimens of radiation and/or chemotherapy. Importantly, two new oral tyrosine kinase inhibitors entrectinib (RXDS-101) and LOXO-10 are undergoing clinical trials in patients with *NTRK* fusion positive tumors. In a recent case report, metastatic SC of salivary gland showed a durable (7 month) partial response to entrectinib [43]. As SC of thyroid becomes an increasingly recognized entity, the use of these directed tyrosine kinase inhibitors will likely increase.

Conclusion

Here we present the eleventh published case of SC of the thyroid gland. Our case represents the first patient with diffuse metastatic disease at presentation and the most aggressive clinical course to date with the patient dying of disease 20 days after presentation from extreme airway compromise, thus closely mimicking undifferentiated/anaplastic thyroid carcinoma. Review of the reported cases suggests that SC of the thyroid may be more aggressive than those arising at other anatomic sites. Whether this changes with increased recognition of this entity and properly targeted therapy (ie; *NTRK*-specific tyrosine kinase inhibitors and *not* radioactive iodine) remains to be seen.

Compliance with Ethical Standards

Conflict of interest The authors report that there are no conflicts of interest to disclose.

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