Mammary Analog Secretory Carcinoma (MASC) Involving the Thyroid Gland: A Report of the First 3 Cases

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Abstract Salivary gland-type tumors have been rarely described in the thyroid gland. Mammary Analog Secretory Carcinoma (MASC) is a recently defined type of salivary gland carcinoma characterized by a t(12;15)(p13;q25) resulting in an *ETV6-NTRK3* fusion gene. We report 3 cases of MASC involving the thyroid gland without clinical evidence of a salivary gland or breast primary; the clinico-pathologic characteristics are reviewed. Assessment for rearrangement of the *ETV6* (12p13) locus was conducted by fluorescence in situ hybridization (FISH) on representative FFPE sections using an *ETV6* break apart probe (Abbott Molecular, Des Plaines, IL, USA). The patients were two females (52 and 55 years-old) and 1 male (74 years-old). The tumors were poorly circumscribed solid white tan nodules involving the thyroid. Histologically, they were invasive and showed solid,

microcystic, cribriform, and tubular growth patterns composed of variably bland polygonal eosinophilic cells with vesicular nuclear chromatin and conspicuous nucleoli. All three cases showed metastasis to lymph nodes; one case showed lateral neck involvement. The tumor cells were positive for S100 and mammaglobin. GATA-3 and PAX-8 were positive in 2 cases, one of which only focally so. All three cases were negative for TTF-1 and thyroglobulin. Rearrangement of the *ETV6* locus was confirmed in all cases and a diagnosis of MASC rendered for each case. A site of origin distinct from the thyroid gland was not identified, with a median follow up of 24 months. MASC may rarely involve the thyroid gland. The origin of these lesions is unknown; while an origin from ectopic salivary gland-type cells is entertained, a metastatic origin from an occult primary cannot be definitively excluded at this time.

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Given the histologic (follicular-like microcystic pattern with colloid-like secretions and papillary pattern), immunophenotypic (PAX-8), and even molecular overlap, MASC can be mistaken for papillary thyroid carcinoma and should be considered in the differential diagnosis of a thyroid mass.

Keywords Mammary analog secretory carcinoma · Thyroid · Salivary gland-type carcinomas · Adenocarcinomas · *ETV6-NTRK3*

Introduction

Salivary gland-type tumors, such as mucoepidermoid carcinoma and sclerosing mucoepidermoid carcinoma, have been rarely described in the thyroid gland [1–4]. Mucoepidermoid-like areas may be found in follicular derived tumors [5, 6]. In the salivary glands, mammary analog secretory carcinoma (MASC) is recently defined neoplasm that is characterized by a *t*(12;15)(p13;q25) resulting in an *ETV6-NTRK3* fusion gene [7–9]. Histologically, MASC is composed of cells with bland nuclei, prominent central nucleoli and abundant, granular to vacuolated eosinophilic cytoplasm. MASC can show a variety of histologic patterns including: microcystic, solid, tubular, and glandular [7, 9]. Associated bubbly intraluminal secretions are typically present [7]. In the salivary gland, the main differential diagnosis of MASC includes acinic cell carcinoma [8, 10]; however, depending on their histologic pattern, these tumors can resemble many other tumors, including adenocarcinoma, not otherwise specified, polymorphous low-grade adenocarcinoma, low grade salivary duct carcinoma, mucin-producing signet ring adenocarcinomas, and mucoepidermoid carcinomas [8]. MASCs are known for having a slightly better behavior than many of their mimics making their identification important [8].

In a recent large series of head and neck MASC, one case involving the thyroid gland was reported [11]. Herein, we present a clinicopathologic series of three MASCs that were centered about the thyroid gland, including two previously unreported cases.

Materials and Methods

Three cases diagnosed as mammary analog secretory carcinoma involving the thyroid gland were identified; one case each occurring at H. Lee Moffitt Cancer Center, Tampa, FL; University of Pittsburgh, Pittsburgh, PA; and University of Alabama at Birmingham (UAB). We reviewed their clinical and pathologic information as well as their histologic and immunohistochemical findings. The

case from UAB had been previously published as part of a large series of head and neck MASC [11]. Using routine methods, immunohistochemical stains were performed on formalin fixed paraffin embedded tissue using the automated immunostainers. FISH analysis was performed on representative 4 micron-thick, formalin-fixed, paraffin-embedded tissue sections on each case using the Vysis LSI *ETV6* (12p13) Dual Color, Break Apart Rearrangement Probe (Abbott Molecular, Downers Grove, IL) as previously described. Strong, well-delineated hybridization signals were independently scored by two individuals in 200 interphase nuclei per specimen. An interphase cell specimen was interpreted as abnormal if splitting of the normally juxtaposed *ETV6* probe signals were detected in >15 % of cells. Images were acquired using the CytoVision Image Analysis System (Applied Imaging, Santa Clara, CA).

Results

The patients were two females (52 and 55 year-old) and one male (74 years-old); the mean age of our patients was 60.3 years. Clinically, all patients presented with a thyroid mass. All patients underwent a total thyroidectomy and lymph node resection. On macroscopic examination, the size ranged from 2.4 to 4 cm; the epicenter of the first two cases was the thyroid gland and the third case involved both the trachea and thyroid gland; whether the tumor arose in the trachea or in the thyroid was not entirely definitive in this case. Extrathyroidal extension was not present in the first two cases (See Table 1). All the tumors were poorly circumscribed solid white tan nodules. Histologically, the tumors showed several overlapping features. All were invasive and showed solid, microcystic, cribriform, tubular and papillary growth patterns composed of polygonal eosinophilic cells with vacuolated cytoplasm with vesicular nuclear chromatin and conspicuous nucleoli. Nuclear grooves were present in all three cases and were frequent in the second and third case. Cellular atypia was mild to focally moderate (See Figs. 1, 2, 3, 4). The first case demonstrated high-grade histologic features in the form of an elevated mitotic rate (10 per 10 high power fields) and cellular necrosis, while the other 2 cases lacked necrosis and exhibited low mitotic rates (3 per 10 hpf and 2 per 10 hpf). The secretions varied in color from pink to pale purple and could easily be mistaken for colloid. Two of the 3 cases showed a prominent lymphoplasmacytic infiltrate. None of the tumors demonstrated a conventional papillary or follicular thyroid carcinoma component (although a separate papillary microcarcinoma was seen in one case). Ectopic benign salivary gland tissue was not seen in any case, however the last case showed tracheal salivary gland

Table 1 Clinical and pathologic findings

Case	Age (years)	Sex	Tumor size (cm)	Tumor site	Lesion Epicenter	Papillary growth	Nuclear atypia	Nuclear grooves	Mitoses Per 10 hpf	IBT	+LN met	ENE	Treatment	Evidence of disease	Follow up (months)
1	74	M	4.0	RUL	Intra-thyroidal	Present, focal	Severe	Yes	10	No	Yes; Central, VI: 0/3 Levels II–V: 3/21	No	Thyroidectomy and right levels II–V and right level VI LN dissection; Radiotherapy and Chemotherapy	Liver metastasis; DOD	12
2	52	F	2.4	Left mid inferior	Intra-thyroidal	Present	Mild	Yes	3	No	Yes; Paratracheal: 1/3 Lateral neck: ND	No	Thyroidectomy and paratracheal LN dissection	NED	26
3	55	F	2.6	Trachea/Left thyroid	Trachea and thyroid	Present, focal	Mild	Yes	2	Yes	Yes; Paratracheal: 5/17 Left Neck: 0/24	No	Thyroidectomy, tracheal resection, and LN dissection; Postoperative radiation	NED	43

DOD death of disease, *ENE* extranodal extension, *F* female, *IBT* involvement beyond thyroid, *hpf* high power fields, *LN* lymph node, *M* male, *NED* no evidence of disease, *ND* not done, *RUL* right upper thyroid lobe, *+LN met*, lymph node metastasis

tissue adjacent to the tumor. All three carcinomas showed metastasis to lymph nodes; one case showed lateral neck involvement.

The secretions were focally positive for mucicarmine and PAS with and without diastase digestion. Mucicarmine stain showed focally positive intracytoplasmic vacuoles. Immunophenotypically, the tumor cells were positive for S100 and mammaglobin in all cases. PAX-8 was diffusely positive in a case and focally positive in another, and negative in the third. All these cases were negative for TTF-1 and thyroglobulin. Rearrangement of the *ETV6* locus was confirmed in all cases by molecular cytogenetic analysis and a diagnosis of MASC rendered for each case (See Table 2). In all the cases, a site of origin distinct from the thyroid gland was not identified. One patient (case 1) developed liver metastasis and died of disease; and two patients are currently alive without evidence of disease,

Fig. 1 Case 1. The tumor showed focally papillary features with well-defined fibrovascular cores (a). Areas with glandular pattern were admixed with the papillary patterned areas. Areas with the “classic” pattern of MASC were also seen; these areas show dense eosinophilic to purple mucin. The nuclei showed prominent red nucleoli and open clear chromatin (b)

Fig. 2 Case 2. This case showed a tumor involving the thyroid. The tumor showed a capsule and hyalinization with a variety of histologic patterns (a); areas with papillary pattern were identified (b). Additionally, the tumor cells showed nuclear clearing and small nucleoli attached to the nuclear envelop resembling a “papillary thyroid carcinoma” (inset; b); a cribriform pattern with glandular spaces filled with *pale pink* to eosinophilic mucinous material resembling colloid was also noted (c); the cells also showed *round* nuclei with prominent nucleoli (inset; c)

Fig. 3 Case 3. The tumor in this case showed the classic cribriform pattern with dense eosinophilic mucin (a). The tumor cells show nuclear grooves and nuclear overlapping resembling a papillary thyroid carcinoma (b)

Fig. 4 Case 1. ETV6 break-apart probe of the tumor involving the thyroid showing disruption of the *orange* and *green* signals and indicating rearrangement of the ETV6 (12p15) locus (Fluorescent in situ hybridization; high power)

with a mean follow up of 27 months (range: 12–43; median: 26 months).

Discussion

The presence of t(12;15)(p12;q25) translocation resulting in the *ETV6-NTRK3* gene fusion was initially identified in congenital fibrosarcoma and later in breast secretory carcinoma [12–15]. The protein product of this abnormality is a constitutively active protein-tyrosine kinase with transformation activity [16]. In 2010, a series of tumors arising from the salivary gland harboring the same translocation were identified; due to their characteristic morphologic features and the similarity to the secretory carcinoma of the breast this tumor was designated as mammary analog secretory carcinoma (MASC) of salivary gland [7]. Later on, additional MASC cases were identified either retrospectively or prospectively [8, 11, 17–21]. Before the MASC characterization, these tumors were previously classified as acinic cell carcinoma, adenocarcinoma, not otherwise specified, mucoepidermoid carcinomas [8, 17, 22] and cystadenomas [23]. We present three distinct cases of MASC involving the thyroid gland, including two previously unreported examples.

The origin of the MASCs involving the thyroid gland is unknown, but there are three possibilities:

- (1) One possibility is that these MASCs represent thyroid follicular epithelium-derived tumors that are simply mimicking a salivary type carcinoma; after all, *ETV6-NTRK3* rearrangement has been reported in papillary thyroid carcinoma, especially in tumors associated with exposure to iodine -131, and there is some morphologic overlap (see discussion below) [24, 25]. Indeed, papillary thyroid carcinomas with features of salivary gland tumors (e.g., mucoepidermoid carcinoma and adenoid cystic carcinoma) have been reported [5, 6, 26]. On the other hand, in the reported papillary thyroid carcinomas with areas mimicking salivary-type neoplasms, there were at least some foci where the tumor is recognizable as a thyroid follicular derived tumor such as conventional-appearing papillary thyroid carcinoma [5, 6, 26]. This is not the case

in these three MASCs; all three cases had a MASC-like appearance throughout. Moreover, the three MASCs were not only histologically identical to MASC of salivary glands, but also demonstrated the same immunophenotype with diffuse S100 and mammaglobin positivity and a complete absence of TTF-1 or thyroglobulin immunoreactivity, therefore making this possibility unlikely. In these cases, the PAX-8 expression may be not specific at all.

- (2) Salivary type carcinomas may involve the thyroid gland secondarily, either by direct extension from the larynx or trachea or via distant metastasis. None of the three patients with thyroid MASC, however, had a history of malignancies elsewhere. Given the somewhat limited follow-up, however, it is not yet possible to entirely exclude the possibility of a distant metastasis from a breast or salivary gland MASC or the possibility of a MASC arising from adjacent tracheal minor salivary glands in case 3.
- (3) Finally, a third possibility is that the MASCs were truly primary to the thyroid gland. Thyroid tumors with morphology similar to their counterparts in the salivary gland are seen occasionally in the thyroid; these include pleomorphic adenoma and mucoepidermoid carcinoma [1–4, 27]. An origin on ectopic rests of benign salivary gland tissue may be entertained as they are rarely seen within the thyroid gland [28]. None of the three MASCs, however, demonstrated evidence of origin from metaplastic or ectopic tissues in the reviewed materials.

Thyroid MASC are too rare to comment on site specific biologic features as their prognosis is not yet known. Here, all three cases demonstrated regional lymph node metastases, and one case exhibited extrathyroidal extension and one case showed high-grade histologic features. This patient died having developed liver metastasis and the other two patients are currently alive without evidence of disease. Additional follow up will be needed to determine their behavior.

A recent case of MASC apparently arising in the thyroid has been reported [29]. Similarly to our cases, this tumor showed microcystic, solid, glandular, and papillary architecture; and the cells nuclei showed prominent nucleoli, nuclear grooves, and rare nuclear pseudoinclusions [29].

Table 2 Immunohistochemical stains and fluorescent in situ hybridization results

Case	TTF-1	TG	PAX-8	S100	Mammaglobin	GATA-3	DOG-1	ETV6 FISH
1	–	–	+, f	+	+	+, f	+, f	+
2	–	–	–	+	+	ND	ND	+
3	–	–	+	+	+	+	+	+

f focal, ND not done, – negative, + positive, TG Thyroglobulin, TTF-1 thyroid transcription factor-1

This tumor was initially diagnosed as “papillary thyroid carcinoma”; on follow up, after local recurrence and widespread metastasis, the tumor cells were found to be positive for GATA-3 and mammaglobin and negative for thyroglobulin and TTF-1. Additionally, this tumor was positive for the ETV6-NTRK3 fusion by RT-PCR [29].

MASC involving the thyroid gland has a significant histologic overlap with a primary thyroid carcinoma, particularly papillary thyroid carcinoma, and represents a significant diagnostic pitfall, as seen in the recently reported case [29]. MASC demonstrates follicular, papillary, and microcystic patterns, along with eosinophilic secretions that may resemble colloid. Moreover, considering how common papillary thyroid carcinoma is compared to how rare MASC involving the thyroid gland is, mistaking the latter for the former would be understandable. Nevertheless, it is important to identify MASC in the thyroid gland because it could represent distant metastatic disease from a breast or salivary gland primary tumor. Even if MASC of the thyroid gland is presumed to be primary, it would likely be treated differently since it would likely not respond to radioactive iodine. The first step in correctly diagnosing MASC in the thyroid gland is recognizing that it may occur in this site. The clues for the diagnosis are the glandular morphology, the bluish pink intraglandular material, and the cytology details. The cells may show grooves; however, the nuclei are round than oval with vesicular chromatin and the cytoplasm may show vacuoles. This histologic, immunophenotypic, and molecular findings are otherwise typical for MASC. Second, immunohistochemistry must be employed. MASC is positive for mammaglobin and usually GATA3, while thyroid follicular epithelial neoplasms are usually negative for these markers. Conversely, MASC is consistently negative for TTF-1 and thyroglobulin. Caution must be used in interpretation of S100 and PAX8; as S100 is often positive in papillary thyroid carcinomas [30, 31], and PAX8 staining was found in 2 of these 3 MASCs involving thyroid gland.

In conclusion, MASC may rarely involve the thyroid gland where it mimics papillary thyroid carcinoma. Given some morphologic, immunophenotypic, and even the potential FISH results overlap between the two tumors, a high index of suspicion and judicious use of immunostains (primarily mammaglobin, GATA3, TTF-1, and thyroglobulin) are needed to distinguish them. Additional follow up will be needed to more conclusively determine their origin (primary vs. metastatic) and significance of MASC in the thyroid gland.

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