Review Article

Secretory carcinoma — impact of translocation and gene fusions on salivary gland tumor

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Abstract

Secretory carcinoma (SC), previously described as mammary analogue secretory carcinoma (MASC), is a recently described salivary gland tumor which morphologically resembles mammary secretory carcinoma. The first description of SC/MASC, reported by Skálová *et al*. in 2010, was as a rare salivary carcinoma imitating secretory carcinoma of the breast. SC/MASC is a unique salivary gland tumor with morphological overlap with acinic cell carcinoma (AciCC), mucoepidermoid carcinoma (MEC), and adenocarcinoma not otherwise specified (ADC-NOS). SC/MASC shares similar clinicopathological features with AciCC. As a critical difference between SC/MASC and AciCC, SC/MASC characteristically has the chromosomal translocation t(12;15)(p13;q25) which leads to a fusion gene between the *ETV6* gene on chromosome 12 and the *NTRK3* gene on chromosome 15. This genetic background is an important differential diagnostic finding for excluding other salivary gland tumors and may be a critical factor determining the prognosis for patients with SC/MASC. Research in recent years has provided a large body of new data on SC/MASC and suggests the possibility that the *ETV6-NTRK3* translocation could be a therapeutic target. Here, we review the morphological and clinicopathological features of SC/MASC and discuss new directions for therapy.

Keywords: Secretory carcinoma; mammary analogue secretory carcinoma; MASC; *ETV6-NTRK3* fusion gene; salivary gland tumor

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Introduction

Secretory carcinoma (SC), previously known as mammary analogue secretory carcinoma (MASC), is a new entity of malignant salivary gland tumor, which is similar to mammary SC in terms of its histologic and genetic features (1,2). Mammary SC is a rare malignancy and is reported to show slow-growing and indolent behavior. It occurs more often in younger women than in elderly women (3). Molecularly, mammary SC is the only epithelial tumor with the t(12;15)(p13;q25) translocation in breast, leading to a fusion of the *ETV6* gene from chromosome 12 and the *NTRK3* gene from chromosome 15 (4,5). The *ETV6-NTRK3* fusion gene encodes a chimeric tyrosine kinase, and this fusion results in a constitutively active chimeric tyrosine kinase mitogenic pathway and the phosphatidyl inositol-3-

kinase (PI3K)-AKT pathway (6,7). In 2010, Skálová *et al*. reviewed 16 salivary gland tumor cases that were previously classified as either acinic cell carcinoma (AciCC) or adenocarcinoma not otherwise specified (ADC-NOS) (8). The authors found that all cases but one were also positive for the *ETV6-NTRK3* translocation. They specified these cases as MASC, indicating a new salivary gland tumor entity. Since the first description of SC/MASC, more than 100 additional cases have been reported (8-20).

Clinical features

Many cases of SC/MASC had been previously classified as AciCC, mucoepidermoid carcinoma (MEC), and ADC-NOS. The most common malignancies reclassified as SC were ADC-NOS (37.8%) and AciCC (12.4%) (9,21). Retrospective studies showed that 19% of parotid gland and 79% of extraparotid gland tumors that were originally diagnosed as AciCC had been reclassified as SC/MASC (14). The site of origin for MASC/SC is the parotid gland in about two-thirds of reported cases; the other sites of origin are the intraoral minor salivary gland and the submandibular gland. Compared to AciCC, SC/MASC appears more often in non-parotid sites. Recent studies suggested that most non-parotid gland tumors diagnosed as AciCC might have a high probability of being reclassified as SC/MASC (13). SC/MASC has a higher incidence of regional lymph node involvement than AciCC (9,15). SC/MASC occurs in both children and adults (13 to 72 years), with an average age of 44.2 years (8-10), and has a slight male predilection, while AciCC predominantly affects women. Based on the previously reported cases, the overall male-to-female ratio was 1.5:1 (9).

Histologic and immunohistochemical features

Histologically, the cells of this tumor consist of the microcystic, tubular, solid, and papillary architecture, and characteristically have abundant extracellular material (1,5,17,22). These growth patterns of tumor cells overlap considerably between SC/MASC and AciCC. The cyst wall may contain a single cell lining, and the cells in these foci often show hobnailing (8,10). The cystic spaces often contain eosinophilic and periodic acid-Schiff staining-positive secretory material. Immunohistochemically, SC/MASC is characterized by strong S-100 protein, mammaglobin, vimentin, whereas AciCC has moderate or weak staining for S-100 protein and vimentin (8). Recent immunohistochemical analyses indicated that DOG1 staining was reliable for differential diagnosis. AciCC was reported to show diffuse DOG1 staining, whereas SC/MASC was negative or focal staining. Combined DOG1 and mammaglobin immunohistochemistry is reported comparable to *ETV6*-breakapart analysis for differentiating between papillary cystic variants of AciCC and SC/MASC (23-25) (*Table 1*). In addition, SC/MASC is known to express GATA3, pan-cytokeratin (AE1-AE3 and CAM5.2), CK7, CK8, CK18, CK19, epithelial membrane antigen (EMA), MUC1, MUC4, STAT5a, GCDFP15, adipophilin, etc., and is reported to be negative for calponin, smooth muscle actin (SMA), CK14, CK5/6, p63, etc. (8,26,27). Even with those immunohistochemical markers, some cases represent diagnostic difficulties. Zymogen-poor AciCC is difficult to be distinguished from SC/MASC without *ETV6*-breakapart analysis.

Gene translocations and gene fusions

Translocations are speculated to occur in about 20% of all cancers. In the salivary gland, four cancers have been reported harboring recurrent translocations (28,29). These include adenoid cystic carcinoma (AdCC), hyalinizing clear cell carcinoma (HCCC), MEC, and the newly identified SC (11,28) (*Table 2*).

SC/MASC harbors a t(12;15)(p13;q25) translocation that results in an *ETV6-NTRK3* fusion product (19). The *ETV6-NTRK3* fusion gene encodes a chimeric tyrosine kinase, and this fusion results in a constitutively active chimeric tyrosine kinase mitogenic pathway and the PI3K-AKT pathway (6,7). This fusion occurred in more than 90% of SC/MASC cases (9,10,28). The fusion protein has transforming activity in multiple cell lineages and might have different effects in different organs, characteristics

Table 1 Genomic and immunohistochemical difference between SC/MASC and AciCC

Item	SC/MASC	AciCC
Genetic alteration		
ETV6 split	+	−
Immunohistochemistry		
Mammaglobin	+	−
S100	++	+
Vimentin	++	+
DOG1	−	+

SC/MASC, secretory carcinoma/mammary analogue secretory carcinoma; AciCC, acinic cell carcinoma.

Table 2 Translocations and gene fusions in salivary gland cancers

Salivary gland cancers	Fusion genes	Translocations
SC/MASC	*ETV6-NTRK3*	t(12;15)(p13;q25)
AdCC	*MYB-NFIB*	t(6;9)(q22-23;p23-24)
HCCC	*EWSR1-ATF1*	t(12;22)(q13;q12)
	CRTC1-MAML2	t(11;19)(q21;p13)
MEC	*CRTC3-MAML2*	t(11;15)(q21;q26)
	EWSR1-POU5F1	t(6;22)(p21;q12)

SC/MASC, secretory carcinoma/mammary analogue secretory carcinoma; AdCC, adenoid cystic carcinoma; HCCC, hyalinizing clear cell carcinoma; MEC, mucoepidermoid carcinoma.

that are also described in infantile fibrosarcoma and acute myelogenous leukemias (22,30,31). *ETV6-NTRK3* translocation has been identified by fluorescence *in situ* hybridization (FISH), reverse transcription-polymerase chain reaction (RT-PCR), or both. For FISH analysis, a dual-color break-apart probe for the *ETV6* gene exhibits a split signal in the nuclei, which indicates that the *ETV6* gene is not intact (19). In analysis utilizing RT-PCR to identify the *ETV6* translocations, the 110-bp fusion transcript of the *ETV6-NTRK3* can be detected (19).

In AdCC, a fusion of the myeloblastosis oncogene (*MYB*) to the transcription factor nuclear factor I/B (*NFIB*) has been identified approximately in one-third or one-half of cases of this carcinoma. It has been demonstrated that *MYB* was overexpressed in the majority of AdCCs, not only in those with *MYB-NFIB* fusions but also in those without the fusion. This suggests that *MYB* may be crucial in the pathogenesis of AdCC (32).

HCCC is a rare, low-grade tumor with a good prognosis. A disease-defining translocation in the Ewing sarcoma RNA-binding protein 1 (*EWSR1*) gene was identified in more than 80% of HCCCs (33). A t(12;22)(q13;q12) translocation produces the most common fusion transcript consisting of the genes *EWSR1* and activating transcription factor 1 (*ATF1*) (28).

MEC harbors t(11;19)(q21;p13) translocation, which produces *CRTC1-MAML2* and less frequently *CRTC3-MAML2* t(11;15)(q21;q26) or *EWSR1-POU5F1* t(6;22)(p21;q12) (9,11,15,29,34). With regard to MEC, the fusion-positive cases tend to have better outcomes, less recurrence, fewer metastases, and lower tumor-related mortality than fusion-negative cases (35). Thus, those salivary tumors are not typically high grade or morphologically heterogeneous.

In addition to the above cancers, pleomorphic adenoma, even though it is a benign mixed tumor, is known to have translocations involving *PLGA1* or *HMGA2* with a high probability (2,11,36).

Therapy for SC/MASC

SC/MASC often progresses slowly and is asymptomatic, and is generally regarded as a low-grade tumor. However, the clinical behavior of SC/MASC ranges from slowly growing tumors that infrequently recur after surgical resection to aggressive tumors that cause widespread metastasis and death. The initial choice of treatment is surgical resection, similarly to other salivary gland tumors. However, some patients with SC/MASC that is regarded as high-grade tumor received radiation therapy or chemoradiotherapy postoperatively (9,15). Although there was no statistically significant difference in the disease-free survival rate between SC/MASC and AciCC, some reports showed that the mean disease-free survival for patients with SC/MASC tended to be worse than that for patients with AciCC (8,9,15). Since the differences between SC/MASC and AciCC are slight in terms of clinicopathological features and outcome, the treatment for SC/MASC should follow those for AciCC. However, SC/MASC has a higher incidence of regional lymph node involvement and more aggressive behavior than AciCC (9,15). Most patients with SC/MASC appear to follow an indolent course, while certain cases appear predisposed to distant metastasis and increased mortality. *ETV6-NTRK3* translocation might have contributed to the clinicopathological difference between SC/MASC and AciCC, therefore, testing for *ETV6* translocation may be essential for the treatment of salivary gland tumors. In addition, *ETV6* translocation may have value in treatment and may represent a therapeutic target in SC/MASC. *ETV6* can fuse with other genes such as *ABL1*, *RUNX1* or *FLT3* (37-39). In leukemia, the fusion of the *ETV6* occasionally responds to TK inhibitors (37,38,40). Additionally, *in vitro* studies of mammary SC showed that insulin-like growth factor receptor 1 (IGFR1) inhibitors might be useful to block *ETV6-NTRK3* translocation-driven oncogenesis (6).

Conclusions

SC/MASC is a salivary gland tumor that is characterized by harboring *ETV6-NTRK3* translocation. In the near future, the identification of translocations and/or gene fusions will be a critical factor in diagnosing salivary gland tumors and

selecting appropriate treatments for them.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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