

Secretory carcinoma of the parotid with adenoid cystic carcinoma cytological pattern: A cytological-pathological correlation with literature review

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A B S T R A C T

Secretory carcinoma (SC) is a rare low-grade malignant tumor, defined by ETV6-NTRK3 fusion, identifiable by FISH. We describe a case in a 58-year-old male with a painless slowly growing 16 mm palpable mass within left superficial parotid. FNA of the mass showed highly cellular specimen with moderate to large pleomorphic cells with round to ovoid nuclei with vesicular chromatin and distinct nucleoli. Cells had moderate to large amounts of vacuolated cytoplasm. Abundant globular metachromatic material, resembling that of adenoid cystic carcinoma, was noted. This material was seen extracellularly and intracytoplasmic, and stained magenta on Diff-Quik and blue-green on Papanicolaou-stained slides. The tumor cells on a cell block preparation were positive for Mammaglobin and S-100. PAS stain highlighted extracellular and intracytoplasmic secretions. FNA diagnosis was “Positive for Malignancy. Morphologic features most compatible with Mammary Analogue Secretory Carcinoma”. ETV6 FISH studies as well as histologic examination of excised tumor confirmed the diagnosis. Finding the globular metachromatic material in SC, that is generally seen in adenoid cystic carcinoma, broadens a cytological differential diagnosis of both entities. Cytological differential diagnosis, clinical, histological, immunohistochemical, and molecular features of secretory carcinomas are discussed in this study.

1. Introduction

Secretory carcinoma (SC) is a low-grade malignant tumor histologically similar to secretory carcinoma of the breast, defined by t(12;15) (p13;q25) translocation, resulting in ETV6-NTRK3 fusion. Most patients with SC present with a slowly growing painless tumor. SC has wide age range (5–77 years) with slight male predilection and occurs most commonly in a parotid gland. SC has moderate risk of local recurrences and lymph node metastases and low risk of distant metastases [1–3]. ETV6-NTRK3 fusion gene encodes a chimeric tyrosine kinase. The same molecular abnormality is present in a subset of acute leukemias and there is a targeted therapy with tyrosine kinase inhibitors, that can be used also for SC treatment [4,5]. We describe a case of a secretory carcinoma with cytomorphological features resembling adenoid cystic carcinoma. To our knowledge, this cytological pattern of MASC has not been previously reported.

2. Materials and methods

Fine-needle aspiration was performed with on-site evaluation of air-dried Diff-Quik (DQ) stained slides and preliminary evaluation of the sample. Three DQ-stained and 3 alcohol-fixed Papanicolaou (Pap) stained direct smears, and cell block preparation with one hematoxylin and eosin (H&E) stained slide were evaluated. Immunohistochemical stains with monoclonal antibodies to S-100 and Mammaglobin were performed on a cell block using an automated immunostainer with appropriate control staining. Clone 4C4.9 S-100 antibodies in 1:750 dilution from Cell Marque were used for S-100 immunohistochemical stain, and clone 304-1A5 Mammaglobin antibodies in 1:150 dilution from Dako were used for Mammaglobin immunohistochemical stain. PAS with and without diastase and Mucicarmine stains were performed using standard laboratory protocol on cell block preparation with appropriate control staining. One-hundred interphase cells from tumor were analyzed using break apart DNA probes from Vysis for the ETV6

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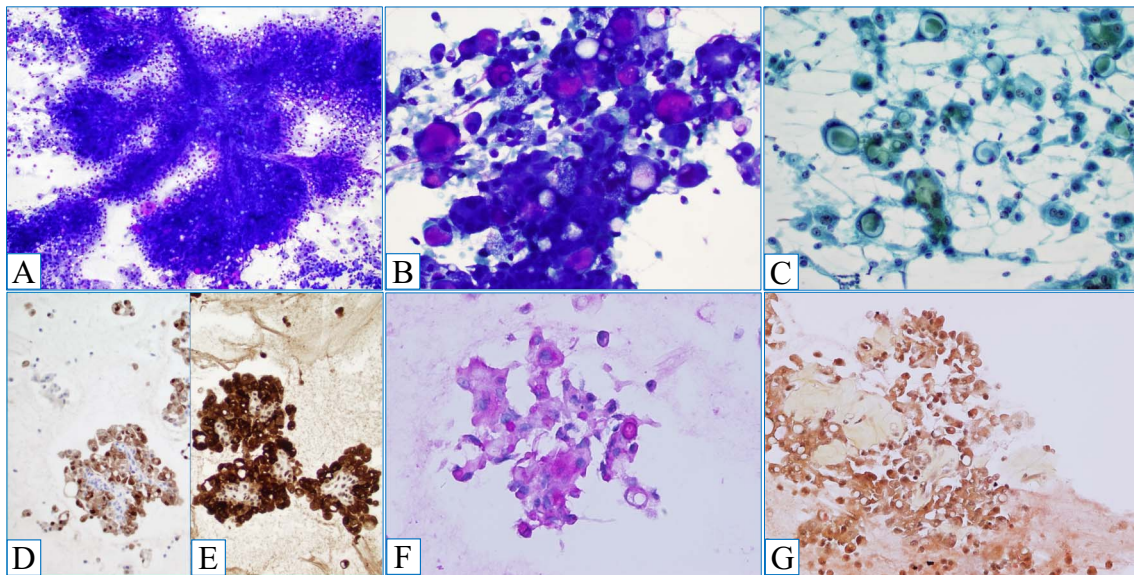


Fig. 1. Composite cytology image. A. Low power magnification showing highly cellular specimen with tumor cells arranged in solid and papillary-like structures (DQ, 10 ×). B. High power view demonstrating moderate to large pleomorphic tumor cells with vacuolated cytoplasm filled with magenta-colored globular material (DQ, 40 ×). C. High power view demonstrating moderate to large pleomorphic tumor cells with vacuolated cytoplasm filled with blue-green globular material (PAP, 40 ×). D. S-100 stain show strong nuclear positivity (IHC, 20 ×). E. Mammaglobin stain show strong nuclear and cytoplasmic positivity (IHC, 20 ×). F. Periodic acid-Schiff–diastase (PAS-D) stain show positivity in the cytoplasmic secretions (40 ×). G. Mucicarmine show negative staining of the tumor cells (20 ×). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

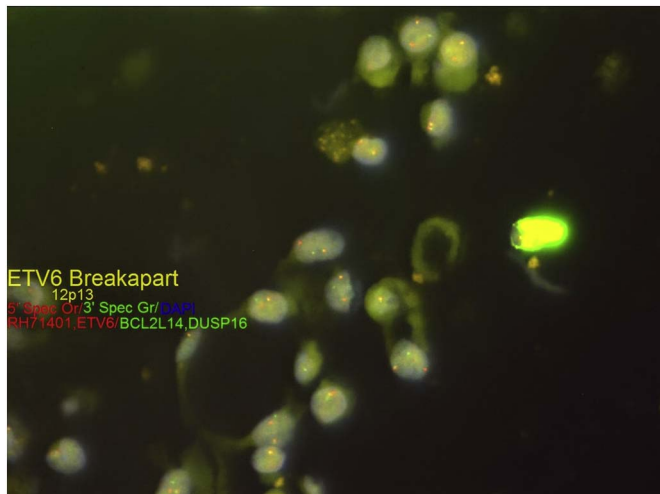


Fig. 2. ETV6 break apart FISH. Red signals (ETV6 gene) and green signals (DUSP16 gene, normally located close to ETV6 gene) are separate, confirming ETV6 rearrangement. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

locus by fluorescence in situ hybridization (FISH) in paraffin-embedded tissue. The entire tumor in the parotid resection specimen was submitted for histologic examination. Histological sections were processed in a standard routine processing algorithm. Tissue was embedded in paraffin, cut on a microtome and stained with H&E.

3. Case report

A 58-year-old male with a history of squamous cell carcinoma of the larynx presented with a palpable 16 mm mass within the posterior superficial lobe of the left parotid gland with cutaneous and subcutaneous involvement based on the CT scan. This lesion has been increasing in size but remained otherwise asymptomatic. Fine needle aspiration (FNA) of the mass was performed.

Cytology slides showed highly cellular specimen with moderate to large pleomorphic cells with round to ovoid nuclei with vesicular chromatin and distinct nucleoli. Cells had moderate to large amounts of vacuolated cytoplasm. Abundant globular metachromatic material, resembling that of adenoid cystic carcinoma, was noted. This material was seen extracellularly and intracytoplasmic, and stained magenta on DQ and blue-green on Pap-stained slides (Fig. 1A, B and C). Immunostains and FISH were performed on cell block preparations. The tumor cells were positive for S-100 and Mammaglobin (Fig. 1D and E). PAS stains with and without diastase highlighted extracellular and

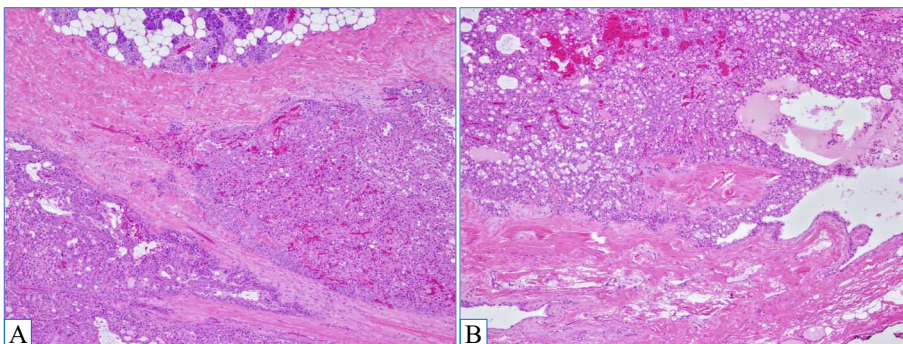


Fig. 3. Composite low power image. Poorly-circumscribed lobulated mass. The tumor has solid (A), tubular and cystic architectural patterns (B). Homogenous eosinophilic secretions are seen within cystic spaces (H&E, 4 ×).

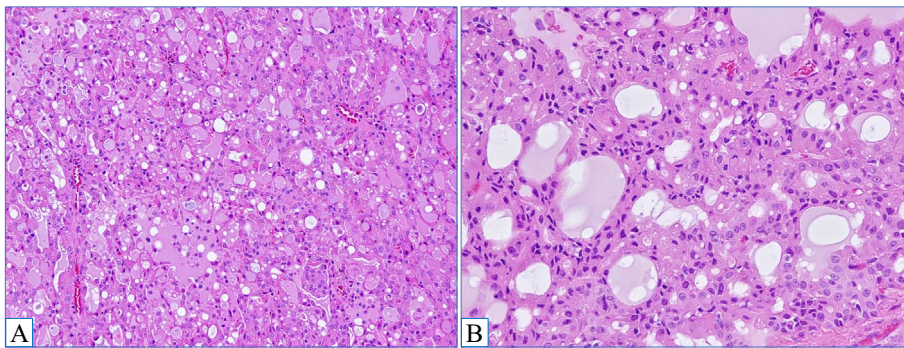


Fig. 4. Composite image. Tubular and solid areas (A and B) with large tumor cells with abundant eosinophilic cytoplasm and eccentric polymorphic nuclei with vesicular chromatin and medium-sized nucleoli. Intra- and extracellular homogenous eosinophilic secretions are seen (H&E, 10 × and 20 ×, respectively).

intracytoplasmic secretions, while mucicarmine was negative (Fig. 1F and G). FNA diagnosis was “Positive for Malignancy. Morphologic features most compatible with Mammary Analogue Secretory Carcinoma”. FISH studies showed ETV6 rearrangement in 68% of 100 cells analyzed, confirming the diagnosis (Fig. 2). Left superficial parotidectomy with 7th nerve dissection and left upper cervical lymph node excision was performed.

Gross examination of the resected parotid gland revealed a 1.4 cm cystic mass filled with green serous fluid and soft yellow material. The entire mass was submitted for histologic examination. Microscopic examination (Figs. 3–4) showed a poorly-circumscribed lobulated, predominantly cystic neoplasm with cystic, solid and tubular architectural patterns. Tumor showed stromal invasion, but no perineural or lymphovascular invasion. Homogenous eosinophilic secretions were seen within tubular structures. The tumor cells were large, had eosinophilic cytoplasm and eccentric polymorphic nuclei with vesicular chromatin and medium-sized nucleoli. Histological features were consistent with the diagnosis of secretory carcinoma, previously rendered on cytology. All surgical margins were uninvolved by invasive tumor. Two lymph nodes (one intraparotid and one upper cervical) were negative for malignancy. The pathologic stage was pT1N0. The patient did not develop any metastatic lesions and there were no signs of recurrence in a one-year follow-up.

4. Discussion

Secretory carcinoma of the breast, formerly known as juvenile breast carcinoma, was first described by McDivitt and Stewart in 1966 in their case series of seven cases [6]. Presence of PAS-positive, extra- and intracellular, homogenous eosinophilic material was a distinctive morphologic feature of those cases. Later a balanced translocation t(12;15)(p13;q25), resulting in ETV6-NTRK3 fusion was found in this entity. Skalova et al. described a tumor with the same morphologic features and molecular abnormality in salivary glands in 2010 [7]. It was named mammary analogue secretory carcinoma or MASC, highlighting its similarity to a breast counterpart. Then in 2017 MASC was renamed to secretory carcinoma (SC) in 4th edition of *WHO Classification of Head and Neck Tumours* to standardize nomenclature in origin sites [8]. Retrospectively, in salivary glands, this entity was often diagnosed as acinic cell carcinoma or adenocarcinomas not otherwise specified. Most cases in John Hopkins University previously diagnosed as zymogen granule poor acinic cell carcinomas and those of non-parotid origin were secretory carcinomas based on ETV6-NTRK3 gene fusion studies [9]. In comparison to acinic cell carcinomas, SC are more likely to occur in non-parotid sites and have higher rate of lymph node metastases and higher T stage at diagnosis [1].

SC usually forms a single, circumscribed but not encapsulated mass, that grossly has rubbery, white to gray cut surface. The mean size of the mass is 2.1 cm (range 0.5–5.5 cm) [3]. Histologically SC can show variety of architectural patterns, including macro- and microcystic, tubular and solid, with extra- and intracellular PAS-positive, diastase-

resistant eosinophilic secretions. There are 3 reported cases of SC with high-grade transformation. Those cases had solid areas with necrosis, nuclear polymorphism, distinctive nucleoli, perineural and skin invasion, and diminished secretory activity [10].

Cytologically SC usually have highly or moderately cellular aspiration smears with variable cellular arrangement patterns, including papillary, sheet-like, follicular, and complex branching clusters on a background of scattered single tumor cells. The cells are generally medium or small in size with abundant vacuolated or granular cytoplasm and mild to moderately atypical oval to round nuclei, that may or may not have distinct nucleoli [11,12]. Based on variable morphology normal parotid gland, acinic cell carcinomas, mucoepidermoid carcinomas, pleomorphic adenomas and myoepithelial neoplasms are frequently in the SC differential on FNA specimens [11]. Some SC FNA specimens show papillary clusters with transgressing vessels, that can resemble normal salivary gland tissue. SC FNA specimens are usually more cellular than normal salivary gland with more scattered single cells. Acinic cell carcinomas have also highly or moderately cellular aspiration smears with large polygonal cells arranged in similar architectural patterns. SC tumor cells demonstrate more size variation of cytoplasmic vacuoles and may show occasional Mucicarmine positivity, but acinic cell carcinomas would stain negative. Low-grade mucoepidermoid carcinomas (MEC) have less cellular aspiration smears composed of multiple cell populations. Some of the tumor cells in MEC may have vacuolated cytoplasm, mimicking SC, but MEC cells more commonly have single cytoplasmic vacuoles, comparing to multiple in SC. It is also unlikely for MEC to have papillary architectural pattern [13,14].

SC tumor cells stain positively for immunohistochemical markers associated with: Mammaglobin, GCDFP15, GATA3, CK7, CK19, vimentin, STAT5a, S100, SOX10, MUC1, MUC4, and negative with: DOG1, p63, p40, CK5/6, SMA, calponin [15–17]. In a differential with acinic cell carcinomas the most useful markers positive in SC are the ones generally associated with breast tissue differentiation: Mammaglobin and GCDFP15; and the most important negative marker is DOG1, that will positively stain tumor cells in acinic cell and adenoid cystic carcinomas.

Secretory carcinomas provide diagnostic challenge for both histologic and cytopathologist due to its rarity and morphologic overlap with other salivary gland tumors, in particular acinic cell carcinomas. It is very important to recognize SC due to its prognostic difference and emerging targeted therapies with tyrosine kinase inhibitors, such as entrectinib and crizotinib [4]. Finding the globular metachromatic material in SC, that is a feature of adenoid cystic carcinoma [18], broadens a cytological differential diagnosis of both entities in FNA specimens. Mammaglobin and S-100 immunostains, and ETV6 break apart FISH were critical in establishing the cytological diagnosis of SC in this case.

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