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Case Report

Salivary Gland Secretory Carcinoma: A Case Report Emphasizing Cytology, Histopathology, and Immunohistochemistry

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ABSTRACT

Secretory Carcinoma (SC) or Mammary Analogue Secretory Carcinoma (MASC) is a recently described tumour of the salivary gland that shares morphological and genetic characteristics with secretory carcinoma of the breast. Due to their complex and heterogeneous presentations, majority of these tumors were previously histologically diagnosed as acinic cell carcinoma or mucoepidermoid carcinoma. Here, we present a case of secretory carcinoma of the parotid gland in a 29-year-old female and discuss the cytological, histological and immunohistochemical characteristics that can be used to diagnose the condition and distinguish it from its histologic mimics.

Keywords: Secretory carcinoma, Salivary gland, Mammaglobin, S-100 protein

INTRODUCTION

Secretory carcinoma of the salivary gland is a recently described rare entity included in the 4th edition of the WHO classification of head and neck tumours.[1] The ductulo-acinar architecture of the breast and salivary glands is shared by the same embryonic ectoderm. In terms of morphology, immunohistochemistry, and genetics, salivary gland secretory carcinoma is similar to breast secretory carcinoma. Secretory carcinoma of the salivary glands was first defined in 2010 by Skalov et al.[2] Previously, it was classified as a zymogen-poor variant of acinic cell carcinoma.[3] Here, we present a case of secretory carcinoma of the parotid gland in a 29-year-old female and discuss the cytological, histological and immunohistochemical characteristics that can be used to diagnose the condition and distinguish it from its histologic mimics.

CASE REPORT

A 29-year-old female presented with a complaint of swelling of the right cheek for 2 months. It was insidious in onset with slow growth. However, since last 2 weeks, she noticed a gradual increase in size, associated with mild pain and dry mouth. She didn't have any complaints of dysphagia, voice change, cough, breathing difficulty, appetite loss, or weight loss. On examination, there was diffuse swelling over the angle of the jaw, which was mobile and soft to firm on palpation. The overlying skin was unremarkable, and there was no facial weakness or paralysis. There was no palpable or apparent evidence of any cervical lymphadenopathy or breast abnormalities. Laboratory investigations were within the normal limits. Ultrasound (USG) showed a small well defined hypoechoic lesion in the superficial lobe of the right parotid gland with multiple mildly enlarged hypoechoic lymph nodes in right level II, III, IV, V. Differentials included lymphoma or salivary gland tumors. USG breasts was normal (BIRADS 1). CT scan of the neck showed a fairly well defined, heterogeneous lesion in the superficial lobe of the right parotid gland, with diffusion restriction and post-contrast enhancement. There was no extension to the deeper lobe of the parotid, indicating a salivary gland neoplasm.

Fine needle aspiration (FNA) showed numerous dispersed tumor cells accompanying sheets and clusters composed of

large polygonal cells with round nuclei, moderate anisonucleosis, small visible nucleoli, and abundant vacuolated to granular pale eosinophilic cytoplasm (Figure-1). Few cells appeared binucleated. There was absence of typical high-grade features such as necrosis and mitoses.

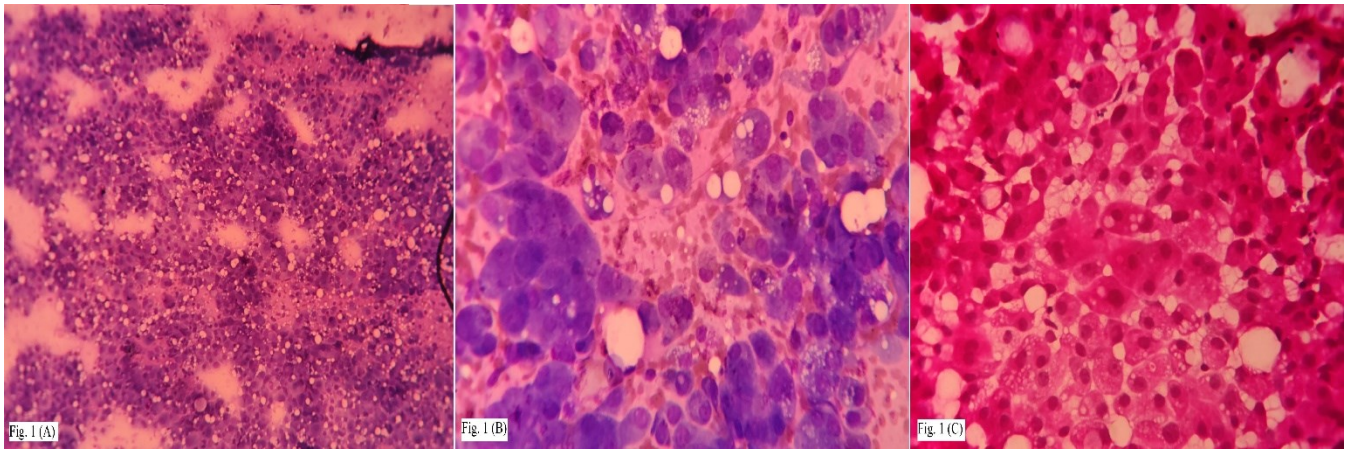

Figure-1: (A) Smear shows loosely cohesive clusters and acinar groups composed of large polygonal cells (MGG, 100 X), (B & C) Smear shows large polygonal cells with round nuclei, moderate anisonucleosis, small visible nucleoli, and abundant vacuolated to granular pale eosinophilic cytoplasm (MGG, 400 X and H & E, 400 X)

Cell block preparation and ancillary testing was done. Cell block showed a tumor arranged in clusters composed of salivary acinar cells displaying round to oval nuclei, exhibiting moderate anisonucleosis with visible nucleoli and moderate to abundant granular eosinophilic cytoplasm.

VENTANA BenchMark IHC/ISH devices were used for immunohistochemistry. The standard antigen retrieval method was Heat Induced Epitope Retrieval (HIER) in Tris-EDTA buffer pH 7.8 at 95°C for 44 min (standard CC1). For IHC, the following antibodies were used:

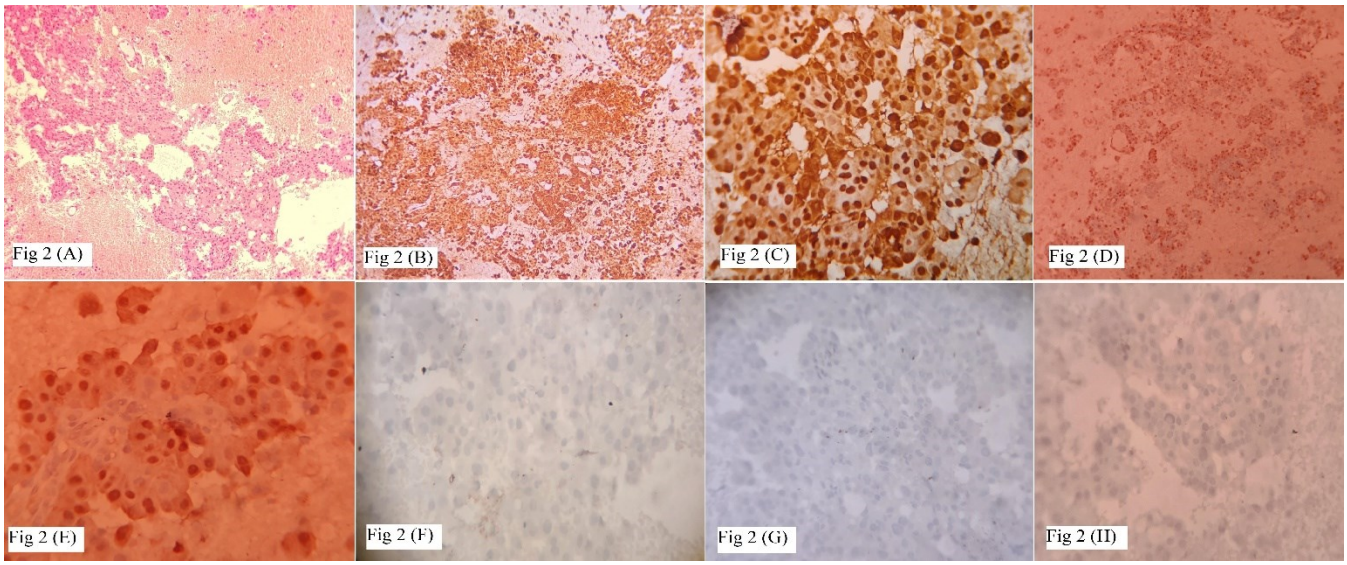

Figure-2: (A) Cell block shows tumor cells arranged as clusters and papillary fragments composed of salivary acinar cells displaying round to oval nuclei, exhibiting moderate anisonucleosis (H&E, 100 X), (B & C) IHC shows tumor cells strong and diffusely positive for mammaglobin, [B (100 X) and C (400 X)], (D & E) IHC shows tumor cells strong and diffusely positive for S100 [D (100 X) and E (400 X)]. (F) DOG1 (400 X), (G) AR (400 X) and (H) P63 (400 X) are negative.

Mammaglobin (31A5) Rabbit Monoclonal Primary Antibody, DOG1 (SP31) Rabbit Monoclonal Primary Antibody, Androgen Receptor (SP107) Rabbit Monoclonal Primary Antibody, Anti-p63 (4A4) Mouse Monoclonal Primary Antibody, S-100 (SP267) Rabbit Monoclonal Primary antibodies were used in formalin-fixed, paraffin embedded tissue and cell blocks stained on VENTANA BenchMark IHC/ISH instruments. Immunohistochemistry shows the tumor cells positive for Mammaglobin and S100, negative for DOG1, P63 and AR (Figure-2).

The final cytology, which was reported as a malignant neoplasm, was most likely of salivary gland secretory carcinoma (Mammaglobin+ve, S100+ve, DOG1-ve, p63-ve, AR-ve). Following that, she underwent a right parotidectomy and a right modified neck dissection. The excised mass was a grey brown nodular measuring 3 x 3 cm which on sectioning revealed a well circumscribed tumor measuring 2.5 x 2.3 x 2.0 cm with a homogenous grey white lobulated cut surface predominantly solid with focal cystic areas. Microscopic examination showed tumor arranged in cribriform and cluster patterns. The neoplastic cells show mildly pleomorphic round to oval nuclei with fine chromatin and few with small distinctive nucleoli. The cytoplasm was pale eosinophilic, granular, and vacuolated. The lobules of the tumor at places were separated by fibrous septa. Pale eosinophilic colloid like intraluminal secretions was also seen (Figure-3 a & b). There was no evidence of mitotic activity or necrosis.

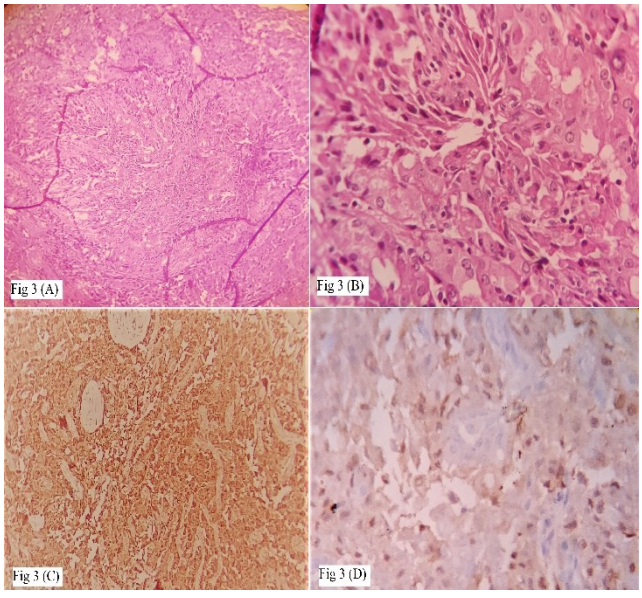

Figure-3: (A) Shows tumor arranged as cribriform and cluster patterns (H & E, 100 X), (B) Shows neoplastic cells having mildly pleomorphic round to oval nuclei with fine chromatin and few with small distinctive nucleoli having abundant pale eosinophilic, granular to vacuolated cytoplasm (H & E, 400 X), (C & D) IHC shows tumor cells strong and diffusely positive for Mammaglobin (200 X) and S-100 (400 X)

Lymph nodes showed reactive changes with no evidence of distant metastasis. Immunohistochemistry was performed, and mammaglobin and S100 were found to be diffusely positive (Figure-3 c & d). A diagnosis of secretory carcinoma was confirmed based on these histomorphological and IHC findings.

DISCUSSION

Secretory Carcinoma is rare, but because it was only recently recognized it is possible that it is currently under-reported or under-recognized. The literature describes only 39 cases of secretory carcinoma of the salivary gland, of which 6 cases are from India and 33 cases from western studies. The male-to-female ratio is 1.5:1, and with a wide age range at presentation (7 to 88 years; mean 46.5 years), it commonly occurs in adults.[2,3] The majority (65%) develop in the parotid gland, followed by the submandibular gland, minor salivary glands, and the airway system. Secretory carcinoma usually manifests as a painless, slow-growing mass. The tumor was originally defined by the recurrent balanced t(l2;15) (p13;q25) chromosomal translocation resulting in ETV6-NTRK3 fusion product, which is detected by a FISH break-apart probe for ETV6.[2]

Cytomorphological features may overlap with other tumors, including acinic cell carcinoma and benign neoplasms of the salivary glands. SC can pose diagnostic challenges on cytology specimens in the Milan System for Reporting Salivary Gland Cytopathology (MSRSGC) without ancillary studies. A definitive diagnosis may be reached only by histologic examination and IHC studies of the excised tumor. Cellular architecture include tight and loosely cohesive clusters, sheets, large and small 3-dimensional papillary groups, numerous single cells, naked nuclei, and transgressing vessels are common cellular arrangements. Neoplastic cells are large-to-medium in size and round-to-polygonal, with moderate-to-abundant cytoplasm. The cytoplasm mainly contains vacuoles. Fine cytoplasmic granules are another cytoplasmic observation. The nuclei are eccentrically or centrally placed, round to oval, with smooth contours, minimal irregularity and one to two prominent nucleoli.[4]

Secretory carcinomas are solitary, well-circumscribed masses that are mostly unencapsulated and have a white-grey, brown, or yellow cut surface. Histologically, secretory carcinoma shares nearly identical growth patterns to acinic cell carcinoma, but instead shows a multivacuolated eosinophilic cytoplasm, often with luminal and intracytoplasmic mucin and no true zymogen granules. Papillary cystic architecture is now considered rare in true acinic cell carcinoma, being far more common in secretory carcinoma. After diastase treatment, both secretory carcinoma and acinic cell carcinoma may exhibit PAS positive, however the pattern in secretory carcinoma is globular (indicative of mucin), whereas it is granular in acinic cell cancer.[5] Secretory carcinoma is S100 and mammaglobin positive, but negative for DOG1, whereas it

is opposite for acinic cell carcinoma.[6] High grade transformation, characterized by nuclear atypia, necrosis, and a lack of secretions, has also been reported in the literature.[7,8]

As many of these tumors were originally classified as acinic cell carcinoma, that is the most common differential diagnostic consideration, but polymorphous low-grade adenocarcinoma, papillary cystadenocarcinoma, mucoepidermoid carcinoma, and low-grade intraductal carcinoma are the most common other considerations. Cases with high grade transformation can mimic Salivary Duct Carcinoma (SDC). The expression of androgen receptor or HER-2/neu and negative staining of S100 protein favors SDC over MASC.[9] A definitive diagnosis can be reached through morphological patterns and immunohistochemistry. Table-1 depicts the various IHC markers that aid in the differentiation of close mimics and help to confirm the definitive diagnosis.[10,11]

Table-1: IHC markers used to differentiate salivary gland tumors[10,11]

	P 63	P 40	S 100	Mamma-globin	Sox 10	DOG 1	GATA 3	AR
Secretory carcinoma	-	-	+	+	+	-	+	-
Acinic cell carcinoma	-	-	-	-	+	+	-	-
PLGA*	+	-	+	-	+	-	-	-
Muco-epidermoid carcinoma	+	+	-	-	-/+	-/+	-	-
Salivary duct carcinoma	-	-	-	-/+	-	-	+	+
Warthin & Oncocytoma	+	-	-	-	-	-	-	-

* PLGA: Polymorphous low-grade adenocarcinoma

Secretory carcinoma is a low-grade malignancy of the salivary glands with an indolent course and a good response to surgical resection. Metastases to regional cervical lymph nodes are uncommon, but one-fifth of cases have been reported. While complete surgical excision with neck dissection is recommended for clinically detected metastases, up to 10% of cases may exhibit high-grade transformation, necessitating additional radio- or chemoradiotherapy. To confirm the diagnosis, a molecular analysis using a polymerase chain reaction (PCR)-based translocation assay is performed. The presence of the characteristic ETV6-NTRK3 fusion confirms the diagnosis. Tyrosine kinase inhibitors could be used for ETV6-NTRK3-positive leukemia.[1,12] Overall, the prognosis remains favorable. Distant metastases are rare. Mortality from SC is rare. The patients are advised to follow-up on a regular basis to be closely monitored for any recurrence.

CONCLUSIONS

In conclusion, secretory carcinoma is a newly described disease entity that affects the salivary glands. The diagnosis can be made by the typical morphological patterns and immunohistochemistry. It can be confirmed in most cases by detecting the ETV6-NTRK3 fusion gene.

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