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Mammary analogue secretory carcinoma of salivary glands: a clinicopathologic study of 11 cases

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ABSTRACT

Mammary analogue secretory carcinoma (MASC) is a recently described tumor sharing the histologic, immunohistochemical, and molecular profile of secretory carcinoma of breast. We aimed to evaluate the morphologic and histochemical features needed/required for the diagnosis of MASC without adjunct of molecular analysis. Six retrospective cases suspicious for MASC and 5 prospective cases reported as MASC were included in the study. Molecular analysis of ETV6 by fluorescence in situ hybridization was performed at the University of Pittsburg, USA. The ages of the patients ranged from 9 to 60 years (mean, 27.5 years). Histologically, all tumors showed mixed growth patterns including microcystic, macrocystic, papillary, tubular, and solid, papillary the being most common pattern. The tumor cells showed round to oval vesicular nuclei with small nucleoli, and eosinophilic to vacuolated cytoplasm. All cases demonstrated luminal and cytoplasmic mucin on periodic acid–Schiff with and without diastase digestion and alcian blue stain. ETV6 fusion gene rearrangement by fluorescence in situ hybridization was detected in 10 of 11 tumors. Recurrences occurred in 3 patients, and 1 patient died of disease 5 years after surgery. In conclusion, MASC is a relatively rare salivary gland malignancy exhibiting distinct histologic and histochemical features which can help to differentiate it from other mimics. Histologically, papillary-cystic and microcystic patterns are the main clues to diagnosis. The follicular pattern of acinic cell carcinoma might represent MASC, as 4 cases in our series had this pattern. Two patients in our series were 9 and 9½ years old respectively, which are the youngest ages ever recorded for MASC.

1. Introduction

Mammary analogue secretory carcinoma (MASC) of salivary glands was first described by Skalova et al [1] in 2010. The tumor was named as such because of its striking morphologic, immunohistochemical, and molecular similarity to secretory carcinoma of breast. They described 16 cases which were previously reported as acinic cell carcinoma (AciCC) or adenocarcinoma not otherwise specified (NOS). Since then, more than 225 cases of MASC have been described in case series and case reports [2–4]. We, herein, describe clinicopathologic features of additional 11 cases of MASC.

2. Materials and methods

We retrieved and reviewed all salivary gland tumors reported as AciCC and polymorphous low-grade adenocarcinoma (PLGA) between 2009 and 2015 in the Section of Histopathology, Aga Khan University Hospital, Karachi, Pakistan. On reviewing the slides, 5 cases of AciCC and 1 case of PLGA that were found to be suspicious for MASC based on established diagnostic morphologic features were selected. Five cases reported as MASC (based on morphology) from 2012 to 2015 in our section were also included in the study.

All cases were fixed in 10% buffered formalin and embedded in paraffin wax. Sections were cut at thickness of 5 μm and were routinely stained with hematoxylin and eosin (H&E). Five-micrometer-thick unstained sections were also cut from paraffin blocks for performing immunohistochemistry (IHC). These unstained sections were deparaffinized in xylene, hydrated in decreasing concentrations of alcohol solution, and then washed in Tris buffer. IHC staining was performed using avidin-biotin-peroxidase method (Sigma, St Louis, MO). The types of antibodies used and results are summarized in Table 1.

Detection of ETS variant 6 (ETV6) gene rearrangement was done by fluorescence in situ hybridization (FISH) on these 11 selected cases in the University of Pittsburg, USA, using a break-apart ETV6 probe (Abbot Molecular, Des Plains, IL) according to the manufacturer's recommendations and interpreted.

3. Results

The ages of the patients ranged from 9 to 60 years (mean, 27.5; median, 23.5 years). There were 7 males and 5 females. The tumor involved

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Table 1
Summary of immunohistochemical stains performed.

Antibody	Dilution	No. of cases tested	No. of positive cases	No. of negative cases
Cytokeratin AE1/AE3	RTU	2	2	0
Cytokeratin 7	1:200	2	2	0
Cytokeratin 20	1:100	2	0	2
Cytokeratin 19	1:50	1	1	0
EMA	1:200	4	4	0
S100	5:1000	5	5	0

RTU indicates ready to use.

the parotid gland in 7 cases, submandibular gland in 3, and the buccal vestibule in 1 case. The size of tumor ranged from 2 to 10 cm (mean, 4.4 cm). The commonest symptom was neck swelling seen in majority of cases. The duration was known in only 2 cases (2 and 4 years, respectively).

Histologically, majority of cases showed a lobulated growth pattern separated by fibrous septa. A combination of microcystic, papillary, tubular, solid, or macrocystic pattern was seen (Fig. 1A). The microcysts contained luminal eosinophilic secretions, whereas tubules and macrocysts showed colloid-like secretions (Fig. 1B and C). Coarse zymogen granules were not seen. In 2 cases, tumor cells showed cytoplasmic vacuolization (Fig. 1D). The papillary growth pattern showed single lining of tumor cells on a fibrovascular core, and tumor cells often showed hobnailing of nuclei (Fig. 2A and B). The macrocysts were lined by solid intraluminal growth pattern (Fig. 2C). The tumor cells were cytologically low grade with small- to medium-sized nuclei containing small nucleoli and pink bubbly cytoplasm. Mitoses were rare to find. Perineural invasion was noted in only 1 case (Fig. 2D). No necrosis was seen in any of the 11 cases. Sparse chronic inflammatory cell infiltrate and hemosiderin pigment were seen in 4 cases. Scattered stromal calcifications were seen in 3 cases, and these were of the psammomatous type in 1 case (Fig. 2E). Single lymph node metastasis was seen in 2 cases in which few lymph nodes were noted histologically. The secretions in both microcysts and tubules showed positivity for periodic acid–Schiff (PAS) with and without diastase digestion and alcian blue (Fig. 3A and B).

Immunohistochemical stains were performed in 10 of 11 cases, and results are summarized in Table 1 (Fig. 3C-E). ETV6 FISH was technically successful in 10 cases and failed in 1 case.

Except for 1 patient, the other patients underwent surgical excision of the tumor. Follow-up was available in 8 of 11 cases, and follow-up period ranged from 17 to 64 months (mean, 40.3 months). Further treatment included chemoradiation and radiotherapy in 2 patients each. Tumor recurred in 3 cases; 1 of these 3 patients having tumor of buccal vestibule experienced 2 recurrences and was reported in another laboratory as seromucinous gland adenoma. The other 2 cases were reported as AciCC. In all these 3 cases, resection specimens had positive surgical margins. Of these 3 patients, 1 patient died of disease 5 years after initial surgery. Two more patients complained of swelling at site of surgery, but no biopsy was taken to confirm recurrence.

4. Discussion

Skalova et al [1] in 2010 described a distinctive low-grade salivary gland tumor which had morphological, immunohistochemical, and molecular features analogous to secretory carcinoma of breast. Both tumor types demonstrate a t(12; 15) translocation involving the ETV6 gene on chromosome 12 and the neurotrophic tyrosine kinase receptor type 3 gene on chromosome 15 [1,5]. Mammary analogue secretory carcinoma of salivary gland, before its recognition, was reported as zymogen granule poor AciCC, cystadenocarcinoma, or adenocarcinoma NOS [1,6]. Since 2010, more than 225 cases of MASC have been reported in the form of case series and case reports [2–4]. The ages of patients in the reported cases ranged from 10 to 86 years [2,3]. The 2 youngest patients

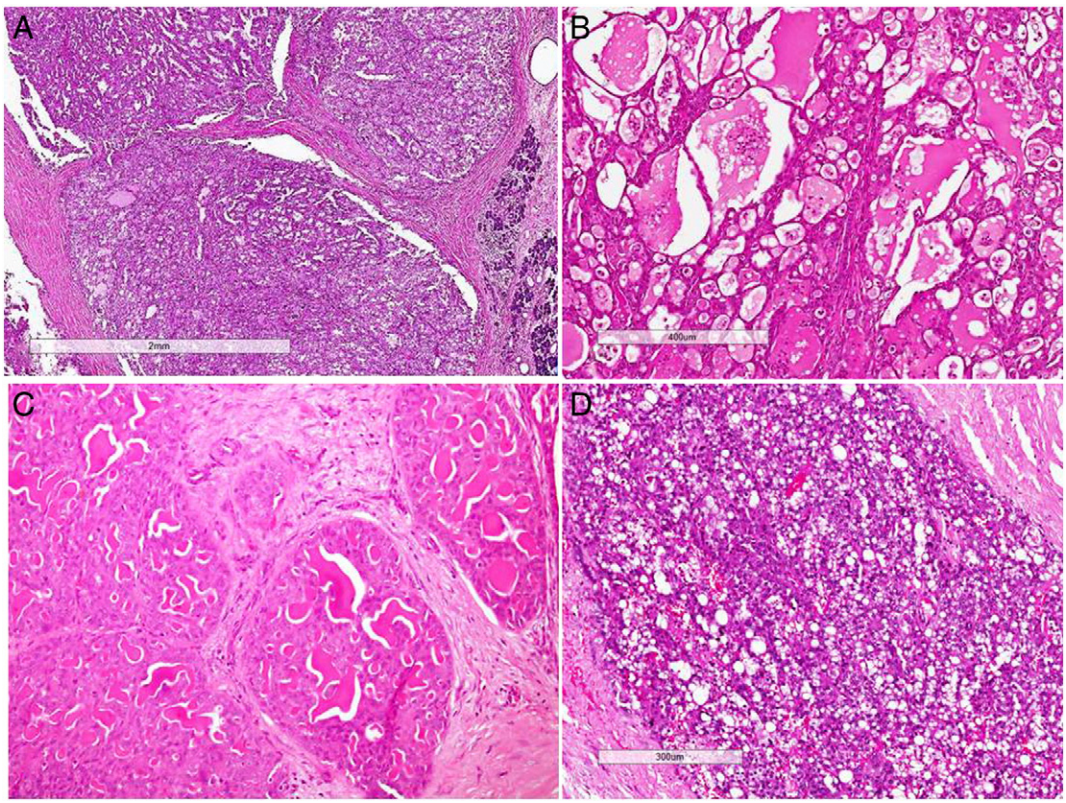

Fig. 1. (A) A typical lobulated architecture of MASC showing a mixture of growth patterns (H&E, 100×). (B and C) MASC with a microcystic pattern filled with abundant pink secretions simulating thyroid follicles. (D) MASC with abundant cytoplasmic vacuolization (H&E, 200× magnification).