Mammary Analogue Secretory Carcinoma

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• Mammary analogue secretory carcinoma (MASC) is a recently described salivary gland tumor that shares the same histologic appearance and ETV6 gene (12p13) rearrangement as secretory carcinoma of the breast. Prior to its recognition, MASC cases were commonly labeled acinic cell carcinoma and adenocarcinoma, not otherwise specified. Despite distinctive histologic features, MASC may be difficult to distinguish from other salivary gland tumors, in particular zymogen-poor acinic cell carcinoma and low-grade salivary duct carcinoma. Although characteristic morphologic and immunohistochemical features form the basis of a diagnosis of MASC, the presence of an ETV6-NTRK3 gene fusion is confirmatory. Given its recent recognition the true prognostic import of MASC is not yet clearly defined.


In the past investigators have noticed histologic similarities between secretory carcinoma of the breast and acinic cell carcinoma (AcCC) of both salivary gland and mammary origin,1,2 and in 2008 it was found that AcCC of the breast lacked the ETV6 gene rearrangement found in secretory carcinoma of the breast.3 Then, in 2010 Skałóva et al4 described a salivary gland tumor that shared the same histologic features and the same recurrent balanced chromosomal translocation t(12;15)(p13;q25) as secretory carcinoma of the breast, and it was distinct from AcCC of salivary gland. They named this new entity mammary analogue secretory carcinoma (MASC).5 This t(12;15)(p13;q25) translocation results in the generation of an ETV6-NTRK3 fusion transcript that is specific to MASC among other salivary gland tumors.6,5 Recognition of MASC as a new entity resulted in a vigorous reexamination by several groups of their archived salivary gland tumor files. These studies revealed that prior to its recognition, MASC was frequently diagnosed as a variety of other salivary gland tumors, most commonly zymogen-poor AcCC and adenocarcinoma, not otherwise specified (NOS).3,2 In the ensuing years, further studies have expanded upon the clinical characteristics, the morphologic features, and the protein expression profile of MASC,8,9 which, as it turns out, is not so rare an entity. Here, we review the current state of knowledge of MASC.

CLINICAL FEATURES

Mammary analogue secretory carcinoma usually occurs in adults but affects patients across a wide age range (13–77 years), with a mean age of about 45 years, and is slightly more common in males.10,11 Cases of MASC affecting pediatric patients have also been described.10 Most patients present with a slow-growing, painless mass with a size of about 2 cm and with a known duration varying from 2 months to several years. Examples presenting with pain and facial paralysis have been described.10 Mammary analogue secretory carcinoma has also been found incidentally at the time of radiologic evaluation for thyroid disease or during routine dental examination.7 Mammary analogue secretory carcinoma involves the parotid gland in about 70% of cases, the submandibular gland in about 7% of cases, and, less commonly, other sites, such as the soft palate, buccal mucosa, base of the tongue, and lip.10

PATHOLOGIC FEATURES

Grossly, MASC is typically a well-circumscribed and unencapsulated tumor with rubbery consistency, gray-white to brown cut surfaces, and a variable cystic component.5 Histologically, MASC is predominantly an extracutaneous and unencapsulated neoplasm typically showing at least some infiltration. Architecturally, MASC may show solid, microcystic, tubular, papillary, and cribriform patterns in varying proportions (Figure 1, A and B). The microcystic growth pattern often contains luminal, eosinophilic colloid-like secretions.3,5,8 Unicystic and multicystic examples of MASC (Figure 1, C) may occur, and these are typically noninfiltrative and may be associated with hemorrhage and cholesterol clefts. Focal intraductal involvement by MASC may occur.8 Similar to translocation-driven sarcomas, the cells of MASC are uniform in nature.5 Cytologically, MASC nuclei are small to medium sized, oval to round, and contain pale chromatin and an occasional single small nucleolus. Characteristically, cytoplasm is abundant and eosinophilic to pink and bubbly (Figure 1, D). Microcystic and tubular spaces are often filled with eosinophilic colloid-like or frothy secretions (Figure 1, B and D).5 Intracytoplasmic, mucicarmine-positive mucin may be found. Importantly, cytoplasmic zymogen granules are absent.5 Mitotic figures are rare, and necrosis is typically absent. Perineural invasion may occasionally be seen, but documented lymphovascular space invasion is very rare. High-grade MASC examples have been reported and are characterized by a more solid and

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trabecular architecture with necrosis, diminished secretions, and larger cells with more prominent nucleoli and atypia. 

Cytopathologic features of MASC in aspirated material have been described. Mammary analogue secretory carcinoma smears show moderate to high cellularity with uniform cells arranged in papillary configuration with transgressing vessels, clusters of cells in an acinar-like configuration, and/or sheets. A variable cystic background and extracellular mucin may be present. Using cytologic preparations, MASC cells are low grade and have been described as ‘‘histiocytoid’’ with abundant, occasionally mucin-filled cytoplasm ranging from vacuolated to granular and eosinophilic. Cell block preparations made from cytology specimens have proved adequate at demonstrating S100 protein and mammaglobin expression by immunohistochemistry and the ETV6 gene rearrangement by fluorescence in situ hybridization (FISH).

Histochemically, the extracellular secretory material stains with mucicarmine, Alcian blue, and periodic acid–Schiff with and without diastase digestion. Immunohistochemically, MASC characteristically shows strong and diffuse expression of mammaglobin (Figure 1, A) and S100 protein. Mammaglobin and S100 protein show greater than 95% sensitivity for MASC but are not specific for MASC, because each may be expressed by several MASC mimickers (see below). Although typically negative, limited DOG1 expression has been described in MASC but when present it is typically limited to the periphery of tumor nests in a noncanalicular pattern. Mammary analogue secretory carcinoma may also express GATA3, pancytokeratin, CK7, CK8, CK18, CK19, epithelial membrane antigen, vimentin, MUC1, MUC4, STAT5a, GCDFP15, and adipophilin, but these are typically not used clinically in the diagnosis of MASC. Mammary analogue secretory carcinoma is typically negative for high–molecular weight keratin and basal cell/myoepithelial markers, such as calponin, SMA, CK14, CK5/6, and p63. However, focal high–molecular weight keratin expression and focal nuclear and cytoplasmic p63 expression have been described in rare cases of MASC.

MOLECULAR FEATURES

The recurrent balanced chromosomal translocation t(12;15)(p13;q25), which results in the fusion of the ETV6 gene on 12p13, a transcriptional regulator, with the NTRK3 gene on 15q25, was first described in MASC in 2003. Since then, the ETV6-NTRK3 breakpoint has been identified in all cases of MASC, and demonstration of this translocation has become the gold standard for diagnosis of MASC. Other fusion partners of ETV6, including NTRK3, NTRK1, NTRK2, and NTRK4, have been identified in rare cases of MASC.
gene on 15q25, a membrane receptor kinase, is so far specific to MASC among other salivary gland tumors. This ETV6-NTRK3 fusion gene encodes a constitutively active chimeric tyrosine kinase with potential oncogenic properties. This molecular aberration can be detected by FISH using a break-apart probe for the ETV6 gene or by reverse transcription–polymerase chain reaction using ETV6 and NTRK3 gene-specific primers. In the context of salivary gland neoplasia, this translocation is specific for MASC. However, several other non–salivary gland neoplasms harbor this rearrangement, including secretory carcinoma of breast, infantile fibrosarcoma, congenital mesoblastic nephroma, and some cases of acute myeloid leukemia.

**DIFFERENTIAL DIAGNOSIS AND ANCILLARY STUDIES**

Reexamination of salivary gland tumor archives by several groups has revealed that many salivary gland tumors, of both low-grade and high-grade types, can show histologic and immunophenotypic overlap with MASC. Below we describe the main entities typically in the differential diagnosis with MASC.

**Acinic Cell Carcinoma**

Acinic cell carcinoma shows overlapping architectural features with MASC, but it typically shows basophilic cytoplasm containing periodic acid–Schiff–positive zymogen granules (“blue dot tumor”; Figure 2). Acinic cell carcinoma typically shows more cytologic diversity than MASC, because serous acinar, intercalated duct–like, vacuolated,
and clear cells can be seen in AcCC. It should be noted that zymogen-poor and intercalated duct–rich examples of AcCC exist, and it is these cases that pose the biggest diagnostic challenge with MASC. However, these cases will be negative for S100 protein and mammaglobin, unlike MASC. Conversely, strong and diffuse S100 protein and mammaglobin expression will virtually exclude AcCC. Further, DOG1 typically shows strong cytoplasmic and canalicular expression in AcCC (Figure 2), favoring MASC because parotid PLGA is rare. In especially problematic cases or in biopsy material, molecular studies may be useful, because no LGSDC has ever been found to harbor the ETV6 gene rearrangement.

**Low-Grade Salivary Duct Carcinoma**

Low-grade salivary duct carcinoma (LGSDC), also known as low-grade cribiform cystadenocarcinoma, displays intraductal proliferations of low-grade ductal cells forming filigreed and anastomosing micropapillae along with loose cribriform and occasional solid patterns analogous to atypical ductal hyperplasia and low-grade ductal carcinoma in situ of the breast (Figure 3). This rare salivary gland tumor can be distinguished from MASC at low-power examination by its predominantly intraductal location. Limited extraductal invasion can, however, be seen in LGSDC. Nuclei of LGSDC are similar to those of MASC, but the cytoplasm of LGSDC is not bubbly or pink, and it often contains yellow lipofuscin-like pigment (Figure 4). Immunohistochemistry will not allow distinction between MASC and LGSDC, because LGSDC also shows strong and diffuse expression of S100 protein and mammaglobin (Figure 3). Low-grade salivary duct carcinoma is exclusively a tumor of major salivary glands, typically the parotid, whereas MASC may also affect minor salivary gland sites. In problematic cases or in biopsy material, molecular studies may be useful, because no LGSDC has ever been found to harbor the ETV6 gene rearrangement.

**High-Grade Salivary Duct Carcinoma**

High-grade salivary duct carcinoma (HGSDC) does not typically enter into the differential diagnosis with cases of low-grade MASC. However, MASC with high-grade transformation may need to be separated from HGSDC. Useful differentiating features are that HGSDC typically shows some intraductal in situ component and displays abundant oncocytoid cytoplasm with well-defined cell borders, unlike MASC. Further, HGSDC is typically more widely infiltrative and displays abundant cribriform architecture with comedonecrosis (Figure 5), which would be unusual in MASC. Because MASC has not yet been shown to harbor an amplified HER2 gene, HER2 gene amplification, a common event in HGSDC, favors HGSDC over MASC. Immunohistochemistry for mammaglobin will not be useful because HGSDC often expresses this antigen.

**Mucoepidermoid Carcinoma**

Mucoepidermoid carcinoma (MEC), with its intermediate, squamoid, and mucin-containing cells, is usually not difficult to distinguish from MASC. However, given that MASC can show mucicarmine-positive cytoplasmic mucin and focally show nuclear p63 expression, macrocystic examples of MASC may on occasion mimic cystic low-grade MEC. Further complicating this issue is that goblet cells in MEC may express mammaglobin. Presence of at least focal squamoid cells, more diffuse nuclear expression of p63, and negative S100 protein expression should allow diagnosis of MEC. In especially problematic cases identifying a CRTC1-MAML2 fusion would be diagnostic of MEC.

**Polymorphous Low-Grade Adenocarcinoma**

Although the low-power gray-blue tumor hue of polymorphous low-grade adenocarcinoma (PLGA), a result of the tumor’s mucinous matrix and the neoplastic cell’s vesicular chromatin, usually allows for the quick elimination of MASC, PLGA not uncommonly coexpresses S100 protein and mammaglobin and usually occurs in minor salivary gland sites, and therefore it could easily enter into a differential diagnosis with MASC, especially on small biopsy specimens. However, the lack of bubbly pink cytoplasm and frequent cordlike and whirling growth patterns of PLGA, among other architectural patterns, should allow for its separation from MASC. ETV6 gene rearrangement study may be necessary in difficult small biopsy specimens, because the ETV6 gene is intact in PLGA. In the context of a salivary gland tumor involving the parotid where the differential is PLGA versus MASC, the parotid location would favor MASC because parotid PLGA is rare.

If histologic, immunphenotypic, and molecular analyses of an ambiguous salivary gland tumor fail to achieve a definitive diagnosis, then a diagnosis of adenocarcinoma, NOS, ultimately a diagnosis of exclusion, may remain prudent.

**Treatment and Prognosis**

Although MASC is currently regarded as a low-grade malignancy with favorable prognosis, it has a potential for an aggressive course. Cases with local recurrence have been reported, suggesting a need for adjuvant radiotherapy in some cases. Cases with high-grade transformation, as well as regional lymph node and distant metastases and death, have been reported, underscoring a need for aggressive management in select cases. However, as with any newly described entity, the data on MASC management, outcomes, and prognostication await large trials with long-term follow up. So far, few studies have investigated this issue. For example, Chiosea et al found lymph node metastasis rates of 17.6% (6 of 34) and 7.9% (3 of 38), respectively, for MASC and AcCC. Given that these same authors found no statistically significant difference in mean disease-free survival for MASC and AcCC (92 and 121 months, respectively), it was stated that at this time MASC and AcCC could probably be treated the same—that is, with excision with or without local radiation therapy. Future investigation of therapeutic strategies specifically targeting the ETV6-NTRK3 chimeric tyrosine kinase may be of use in select cases.

**Conclusions**

Mammary analogue secretory carcinoma is a recently recognized malignant salivary gland tumor that harbors an ETV6-NTRK3 translocation and closely resembles secretory carcinoma of the breast. Before its recognition, MASC was most often diagnosed as AcCC or adenocarcinoma, NOS. Zymogen granule–poor acinic cell carcinoma constitutes the main differential diagnostic consideration. Although there are significant differences histologically between MASC, AcCC, and LGSDC, these entities may on occasion show considerable morphologic overlap. However,
diffuse expression of S100 and mamaglobin by a carcinoma of salivary gland origin virtually excludes AcCC. Similarly, diffuse strong DOG1 expression in a cytoplasmic and canalicular pattern excludes MASC and LGSDC. Because both MASC and LGSDC share S100 and mamaglobin coexpression, histologic exam will be needed to separate these two entities.

Because one study found a 95% concordance rate between using only histology and immunophenotypic profile of MASC but were negative for an ETV6 gene rearrangement as identified by FISH, in most cases an accurate diagnosis of MASC can be made without molecular testing; that is, histology is the basis for a diagnosis of MASC. In difficult cases, however, molecular study for ETV6 could serve as a final arbiter for differentiating MASC from its mimickers, with the caveat that rare cases have been described that have otherwise met the histologic and immunophenotypic profile of MASC but were negative for an ETV6 gene break by FISH. Similarly, cases of morphologic MASC have been positive for an ETV6 gene break by FISH but were negative for an ETV6-NTRK3 fusion by reverse transcription–polymerase chain reaction, suggesting alternate fusion partners in some cases. At the present time no clinical differences have been shown to exist between cases that meet morphologic criteria for MASC but are fusion negative and cases of fusion-positive MASC.

Accurate understanding of the clinical behavior and prognostication of MASC awaits further clinical research, but so far MASC appears to be a low-grade carcinoma with behavior similar to acinic cell carcinoma and a generally favorable prognosis. A potential exists for disease progression and aggressive clinical course in a small number of cases.

References