Unmasking MASC: Bringing to Light the Unique Morphologic, Immunohistochemical and Genetic Features of the Newly Recognized Mammary Analogue Secretory Carcinoma of Salivary Glands

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Received: 15 November 2012 / Accepted: 8 January 2013 / Published online: 5 March 2013
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Abstract Mammary analogue secretory carcinoma (MASC) is a recently described salivary gland neoplasm that is characterized by its striking morphologic and molecular similarities to secretory carcinoma of the breast. This review highlights the characteristic clinical, histologic, immunophenotypic, and molecular features of MASC, and draws attention to the differential diagnosis of this increasingly recognized tumor.

Keywords Mammary analogue secretory carcinoma · Secretory carcinoma · Acinic cell carcinoma · ETV6–NTRK3 · Mammaglobin

Introduction

In 2010, Skálová, et al. [1] published a series of 16 primary salivary gland carcinomas that bore a striking histologic resemblance to secretory breast cancer. In addition, the authors found that these salivary gland tumors shared the immunophenotype and, remarkably, the characteristic *ETV6–NTRK3* translocation of secretory breast carcinoma, and they accordingly designated them “mammary analogue secretory carcinomas” (MASCs). Since the initial description, MASC has been increasingly recognized, with 70 additional reported cases [2–15].

Discussion

Clinical Features

In the initial description of MASC, the vast majority (13 of 16) of cases arose in the parotid gland [1], but subsequent publications have shown that while the parotid gland is the most common site of origin ($n = 50$), MASC may also arise in the oral cavity ($n = 27$), submandibular gland ($n = 8$), and accessory parotid gland ($n = 1$) [1–15]. In the oral cavity, the lip ($n = 9$), soft palate ($n = 8$), and buccal mucosa ($n = 5$) are the most commonly affected subsites [1, 2, 4, 7, 11, 12]. MASC presents most often as a slow-growing, painless mass [1–3, 7]. Unlike secretory breast carcinoma, which is usually seen in young patients, MASC generally occurs in adults (mean 47 years, range 14–78). Surprisingly, MASC is encountered more often in men than women, though the male predominance (46 of 86, or 53 %) [1–15] is not as pronounced as was initially reported [1, 8, 15].

Pathologic Findings

Grossly, MASCs tend to be solitary, unencapsulated but generally well-circumscribed masses that are white–grey, brown, or yellow [3, 4, 9, 14]. MASCs may grossly have a prominent cystic component that exudes fluid upon sectioning [3, 4]. Tumor sizes have ranged from 0.2 to 5.5 cm, with an average size of 1.7 cm [1–11, 15]. MASCs of the oral cavity tend to be smaller (mean 0.9 cm) than those arising in the parotid or submandibular glands (mean 2.2 cm) [1–11, 15]. At the histologic level, MASC is not highly infiltrative, particularly in cases where MASC is predominantly macrocystic. Perineural invasion is uncommon, and lymphovascular invasion has not been reported. MASC is architecturally variable, and may grow

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as back-to-back tubules or microcysts, papillae, or macrocysts (Fig. 1). Secretions are almost always present in the microcysts and/or macrocysts of MASC; they vary from lightly pink and frothy to brightly eosinophilic and colloid-like (Figs. 1, 2, 3). The tumor cells have an apocrine appearance, with granular eosinophilic cytoplasm that often has a vacuolated or “bubbly” quality that may impart a clear cell appearance (Figs. 1, 2, 3). Tumor nuclei are oval, with open chromatin and a single, variably-prominent nucleolus. Mitotic rates are low, usually 0–1 mitotic figures/10 high-powered fields, and necrosis is absent.

The cytopathologic features of a handful of MASCs have been described [3, 5, 6, 14]. Smears were variably cellular and demonstrated both intact tissue fragments with isomorphic cells arranged in a sheet-like or papillary configuration as well as dispersed and dissociated cells with a “histiocyte-like” appearance with large cells containing abundant vacuolated cytoplasm [3, 5, 6].

Special Stains/Immunohistochemistry

The secretory material of MASC is characteristically positive for mucicarmine and periodic acid-Schiff (PAS) with and without diastase digestion. Mucicarmine may highlight focal intracellular mucin [11]. It should be noted that MASC may exhibit occasional PAS-positive/diastase-resistant cytoplasmic material [4, 15]. However, these PAS-positive inclusions are larger and more globular than the fine granules characteristic of acinic cell carcinoma [4].

MASC is consistently immunoreactive for cytokeratin 7, cytokeratin 18, S-100 protein, vimentin, mammaglobin, and STAT5a, generally in a diffuse and strong fashion (Fig. 3) [1–3, 7, 11]. Staining for GCDFP and EMA is also common. P63 may label focal tumor cells [11, 16], but smooth muscle actin and calponin are consistently negative; all three myoepithelial stains may in some cases reveal a peripheral rim of positive cells, suggesting an intraductal component [7, 11]. Like secretory breast cancer,

MASC is negative for estrogen receptor and progesterone receptor [1].

Molecular Diagnostics

MASC characteristically harbors a balanced chromosomal translocation, t(12, 15) (p13;q25), resulting in the formation of the ETV6–NTRK3 fusion gene that encodes a chimeric oncoprotein tyrosine kinase. Interestingly, the same translocation is encountered not only in secretory breast carcinoma [17], but also infantile fibrosarcoma [18], congenital mesoblastic nephroma [19], and some cases of myelogenous leukemia [20]. The chromosomal alteration may be detected by break-apart ETV6 fluorescent in situ hybridization (FISH) (Fig. 3d) or by detecting the ETV6–NTRK3 fusion transcript by reverse transcription-polymerase chain reaction (RT-PCR).

Differential Diagnosis

Studies that have identified MASC retrospectively have found that they were previously most often diagnosed as acinic cell carcinoma (ACC), mucoepidermoid carcinoma, or adenocarcinoma/cystadenocarcinoma, not otherwise specified (NOS) [1–3, 7, 8, 10, 15]. The resemblance of MASC to ACC is particularly striking: both tumors show a variety of overlapping architectural patterns (microcystic, follicular, papillary-cystic), and MASC cells can resemble many of the variety of cell types seen in ACC (intercalated duct-like, vacuolated, non-specific glandular, clear cells). Indeed, we recently found that 19 % of parotid gland tumors previously diagnosed as ACC, and a remarkable 79 % of extra-parotid tumors diagnosed as ACC, were actually MASCs [2]. However, even though the cytoplasm of MASC cells may be granular or even have rare PAS-positive globules (as discussed above), the distinct blue-purple zymogen granules that characterize ACC are not seen in MASC (Fig. 2). Accordingly, the historical practice

Fig. 1 Mammary analogue secretory carcinomas (MASCs) usually exhibit microcystic (a) and/or papillary-cystic (b) growth patterns. Eosinophilic secretory material is present in the microcystic and macrocystic spaces

Fig. 2 At low-power, MASC (a) is histologically indistinguishable from this microcystic-patterned ACC (b). However, at high-power, MASC (c) lacks the basophilic cytoplasmic granules that define ACC (d)

Fig. 3 The cells of mammary analogue secretory carcinoma (MASC) may have a vacuolated cytoplasm that can impart a somewhat clear cell appearance (a). MASC cells and secretions characteristically exhibit strong immunostaining for S-100 (b) and mammaglobin (c).

ETV6 break-apart FISH demonstrates one intact gene (i.e., orange and green together creating a yellow fusion signal) and one rearranged ETV6 gene (d)

of classifying a salivary gland tumor as ACC on the basis of architectural patterns but without clear-cut zymogen granules is probably no longer warranted. A cystic and/or microcystic MASC with vacuolated or clear cells and even focal mucicarmine positivity may be confused with low-grade mucoepidermoid carcinoma, however, MASC lacks the squamoid cells and abundant mucocytes of that are typical of that malignancy [5, 7, 11, 15]. Finally, by definition, a specific entity like MASC must be excluded before arriving at the diagnosis of adenocarcinoma/cystadenocarcinoma, NOS.

While a definitive diagnosis of MASC rests on documentation of its characteristic *ETV6–NTRK3* gene fusion, performing this highly-specialized testing is not feasible for most laboratories. In light of this fact, we believe that a diagnosis of MASC may be made with a salivary gland tumor that exhibits the classic histology of MASC along with strong staining for mammaglobin and S-100, two widely-available immunostains. However, in the absence of archetypal microscopic features, these markers should not be used as surrogates for molecular testing. After all, S-100 is known to be positive in many salivary gland tumors, and the specificity of mammaglobin for MASC is not yet known. It is worth noting, as well, that MASC may not be absolutely defined by the *ETV6* rearrangement. Indeed, one of the original reported MASCs was actually translocation-negative [1], and secretory breast carcinomas are occasionally negative as well [17].

Treatment and Prognosis

The relatively low number of cases of MASC with significant follow-up information limits the evaluation of its prognosis and response to treatment. The therapies employed for cases identified retrospectively have been extremely variable and have ranged from simple excisions to radical resections with or without neck dissections, adjuvant radiotherapy, and/or adjuvant systemic chemotherapy [1, 7]. MASC is currently regarded as a low-grade carcinoma, and its prognosis appears to be favorable overall. However, like ACC and other low-grade salivary gland carcinomas, MASC does have the capacity to behave aggressively on occasion in the form of recurrences, regional lymph node metastases, and even disease-related deaths [1, 7]. For these aggressive cases, the *ETV6–NTRK3* translocation represents an attractive potential therapeutic target, considering that some *ETV6–NTRK3*-positive leukemias have responded to tyrosine inhibitors [7, 21].

The ramifications of misclassifying MASC as ACC, its closest mimicker and also a low-grade carcinoma, are unclear because historical studies investigating ACC almost certainly included a number of MASCs. Chiosea et al. [7] found an increased rate of lymph node metastases

in translocation-positive MASCs when compared to translocation-negative ACCs. However, the difference was not statistically significant, and there were no differences in disease-free survival. In our experience with extraparotid MASCs diagnosed as ACC, the clinical significance of the misclassification was minimal: only 1 of 11 MASCs recurred and none metastasized [2]. This low-grade behavior was similar to the indolent behavior reported for intra-oral ACCs [22–25].

Summary

Mammary analogue secretory carcinoma is a newly-described salivary gland carcinoma that is defined by its histologic, immunophenotypic, and genetic similarities to secretory breast carcinoma. MASC exhibits predominantly microcystic and papillary-cystic growth patterns, and its cells have a bland, apocrine appearance. MASC may be distinguished from ACC—its closest morphologic mimic—by its absence of zymogen granules, positive staining for mammaglobin and S-100, and demonstration of its characteristic *ETV6–NTRK3* translocation. Additional studies are needed to clarify whether the clinical behavior of MASC matches the tumor's low-grade histologic appearance.

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