Published in final edited form as:
Hum Pathol. 2013 October ; 44(10): 1982–1988. doi:10.1016/j.humpath.2013.03.017.

Utility of Mammaglobin Immunohistochemistry as a Proxy Marker for the ETV6-NTRK3 Translocation in the Diagnosis of Salivary Mammary Analogue Secretory Carcinoma

Justin A. Bishop, M.D.[1], **Raluca Yonescu, M.D.**[1], **Denise Batista, Ph.D.**[1], **Shahnaz Begum, M.B.B.S., Ph.D.**[1], **David W. Eisele, M.D.**[2], and **William H. Westra, M.D.**[1,2,3,*]

[1]Department of Pathology, The Johns Hopkins Medical Institutions, Baltimore, Maryland
[2]Department of Otolaryngology/Head and Neck Surgery, The Johns Hopkins Medical Institutions, Baltimore, Maryland [3]Department of Oncology, The Johns Hopkins Medical Institutions, Baltimore, Maryland

Abstract

Mammary analogue secretory carcinoma (MASC) is a recently described salivary gland neoplasm defined by *ETV6-NTRK3* gene fusion. MASC's morphologyis not entirely specific and overlaps with other salivary gland tumors. Documenting *ETV6* rearrangement is confirmatory, but most laboratories are not equipped to perform this test. As MASCs are positive for mammaglobin, immunohistochemistry could potentially replace molecular testing as a confirmatory test, but the specificity of mammaglobin has not been evaluated across a large and diverse group of salivary gland tumors. One hundred-thirty-one salivary gland neoplasms were evaluated by routine microscopy, mammaglobin immunohistochemistry, and *ETV6* break-apart fluorescent in situ hybridization. The cases included 15 MASCs, 44 adenoid cystic carcinomas, 33 pleomorphic adenomas (PAs), 18 mucoepidermoid carcinomas, 10 acinic cell carcinomas, 4 adenocarcinomas not otherwise specified, 3 polymorphous low-grade adenocarcinomas, 3 salivary duct carcinomas, and 1 low-grade cribriform cystadenocarcinoma. All 15 MASCs harbored the *ETV6* translocation and were strongly mammaglobin-positive. None of the 116 other tumors carried the *ETV6* translocation, however mammaglobin staining was present in 1 of 1 (100%) low-grade cribriform cystadenocarcinoma, 2 of 3 (67%) polymorphous low-grade adenocarcinomas, 2 of 3 (67%) salivary duct carcinomas, 2 of 18 (11%) mucoepidermoid carcinomas, and 2 of 33 (6%) pleomorphic adenomas. Mammaglobin is highly sensitive for MASC, but immunostaining can occur in a variety of tumors that do not harbor the *ETV6* translocation. Strategic use of mammaglobin immunostaining has a role in the differential diagnosis of salivary gland neoplasms, but it should not be indiscriminately used as a confirmatory test for MASC.

Keywords

Mammary analogue secretory carcinoma; mammaglobin; acinic cell carcinoma; *ETV6-NTRK3*

[*]Address correspondence to: Justin A. Bishop, M.D., The Johns Hopkins University School of Medicine, 401 N. Broadway, Weinberg 2249, Baltimore, MD 21231, Telephone (410) 955-8116, Facsimile (410) 955-0115, jbishop@jhmi.edu.

Introduction

Mammary analogue secretory carcinoma (MASC) is a salivary gland neoplasm that was first reported in 2010 [1]. MASC is defined by its close resemblance to secretory breast carcinoma, particularly at the genetic level where both tumors characteristically harbor the balanced translocation t (12;15) (p13;q25) resulting in the *ETV6-NTRK3* fusion gene. Since its initial description, 70 additional cases of MASC have been reported, with many of these studies highlighting its propensity to be confused with other tumor types based on overlapping morphologic features [2–15]. Distinguishing MASCs from other salivary gland tumors is important. Not only may these tumors differ from other salivary gland neoplasm with respect to clinical behavior, but the consistent presence of a specific chromosomal translocation may provide a target for biological therapy.

The histologic features of MASC include a microcystic and/or papillary-cystic architecture, an apocrine cellular appearance with abundant pink cytoplasm and uniform bland nuclei, and abundant extracellular secretory material [2–15]. Although these features are consistently present in MASCs, they are not very specific, and overlap with other salivary gland tumors including acinic cell carcinomas, mucoepidermoid carcinomas, adenocarcinomas not otherwise specified (NOS) and low-grade cribriform cystadenocarcinomas. Indeed, we recently noted that most (79%) of alleged acinic cell carcinomas of non-parotid origin actually represent misclassified MASCs [2]. As a result, recognition of MASC and distinction from other tumor types would benefit from the availability of ancillary diagnostic tests.

Diagnostic confirmation of MASC currently requires documentation of the t (12;15) (p13;q25) translocation, but most diagnostic surgical pathology laboratories are not equipped for molecular testing. The observation that MASC, like its counterpart in the breast (i.e. mammary secretory carcinoma), consistently expresses mammaglobin provides a more practical immunohistochemical approach that may obviate the need for more sophisticated testing [16–18]. The purpose of this study was to determine the specificity of mammaglobin staining and establish its reliability as a proxy marker for the *ETV6* rearrangement across a large and diverse group of salivary gland tumors.

Materials and Methods

Cases

Four tissue microarrays (TMAs) were previously constructed from various benign and malignant salivary gland epithelial neoplasms resected at the Johns Hopkins Hospital. These microarrays included 54 adenoid cystic carcinomas, 33 pleomorphic adenomas, 29 mucoepidermoid carcinomas, 11 acinic cell carcinomas, 5 adenocarcinomas NOS, 5 polymorphous low-grade adenocarcinomas, 4 MASCs, 3 salivary duct carcinomas, and 1 low-grade cribriform cystadenocarcinoma. All tumors were obtained from routine formalin-fixed paraffin-embedded blocks. Multiple core samples were taken from each block to address the issue tumor heterogeneity. To increase the number of MASCs, we retrieved tissue blocks from an additional 11 MASCs that were not part of the original TMAs. The MASCs were diagnosed on the basis of morphologic, immunophenotypic, and molecular features as previously described [2, 3]. The remaining salivary gland tumor types were classified on the basis of their histologic and in some cases also immunophenotypic features as defined by the World Health Organization classification of salivary gland tumors [19].

Fluorescence in situ hybridization

Fluorescence in situ hybridization (FISH) was performed on FFPE tissue sections using a commercially available *ETV6* dual color break apart probe (07j77-001, Abbott Molecular,

Des Plaines, IL), as previously described [2, 3]. Cells with rearrangements for *ETV6* had one normal fusion signal and one orange and one green signal at a distance from each other. Tumors with >12% of cells exhibiting rearrangement were considered positive.

Immunohistochemistry

Immunohistochemical staining for mammaglobin (clone 304-1A5; DAKO GenPoint, Carpinteria, CA; 1:200 dilution) was performed on five-micron sections prepared from formalin-fixed and paraffin embedded (FFPE) tissue using standard autostaining protocols on a Ventana Benchmark XT autostainer (Ventana Medical Systems, Inc. Tucson, AZ). Deparaffinization and antigen retrieval (i-view detection system; Ventana) were carried out as an automated program of the Ventana autostainer. Immunohistochemistry was only analyzed on those tumors where ETV6 FISH was successfully performed. For each tumor, the presence of any cytoplasmic immunoreactivity was regarded as positive. For those tumors from the TMA that were positive, whole tissue slides were then evaluated to further quantify the proportion (<50% vs. ≥50%) and intensity (weak vs. moderate vs. strong) of tumor staining.

Results

As previously reported, all 15 MASCs were positive for the *ETV6* rearrangement by FISH [2, 3]. All of the MASCs exhibited the classic morphologic features of MASC including minimal infiltration, microcystic and/or papillary cystic growth patterns, intraluminal secretions, and a monotonous population of eosinophilic cells (Figure 1). FISH was successfully performed in 131(84%) of the tumors. In the remaining 25 cases, FISH failed due to tissue degradation and/or limited cellularity. The *ETV6* translocation was identified in all 15 MASCs, but it was not identified in any of the other types of salivary gland tumors (100% vs. 0%, $p < .0001$, Fischer's exact).

The mammaglobin immunohistochemistry results are summarized in Table 1. All 15 MASCs were immunoreactive for mammaglobin. In each case staining was strong and diffuse, ranging from 50 to 100% of cells (mean, 91%). Staining was present in both the cytoplasm of the tumor cells and in the intraluminal secretory material. Mammaglobin immunostaining was also observed in 9 of 116 (8%) salivary gland tumors that did not harbor the *ETV6* rearrangement including 1 of 1(100%) low-grade cribriform cystadenocarcinoma, 2 of 3 (67%) polymorphous low-grade adenocarcinomas, 2 of 3(67%) salivary duct carcinomas, 2 of 18 (11%) mucoepidermoid carcinomas, and 2 of 33 (6%) pleomorphic adenomas. The staining in these tumors was generally strong, but the proportion of cells staining varied considerably from 5% to 100%. Notably, all of the mammaglobin-positive tumors that were negative for *ETV6* rearrangement exhibited classic morphologic features of their respective tumor types, and none of these tumors displayed classic histologic features of MASC. All adenoid cystic carcinomas (n=44), acinic cell carcinomas (n=10), and adenocarcinomas NOS (n=4) were mammaglobin negative. Overall, mammaglobin was 100% sensitive and 92% specific for the presence of an *ETV6* rearrangement.

Discussion

An increasingly large number of neoplasms are now recognized to be associated or defined by chromosomal rearrangements. Among salivary gland tumors, subsets of mucoepidermoid carcinoma, adenoid cystic carcinoma, and hyalinizing clear cell carcinoma are known to harbor translocations [20]. Mammary analogue secretory carcinoma (MASC) is a recently described salivary gland tumor that is defined by its morphologic and genetic similarities to the secretory variant of ductal breast carcinoma including the presence of the balanced

translocation t (12;15) (p13;q25) resulting in the *ETV6-NTRK3* fusion gene [1]. Detection of this translocation is useful in confirming the diagnosis of MASC, but its value is offset by the reality that most surgical pathology laboratories are not equipped to perform *ETV6* testing. Diagnostic confirmation of MASC would greatly benefit from the availability of more practical and widely available diagnostic assays.

Like its counterpart in the breast, MASCs express mammaglobin at levels that can be easily detected by routine immunohistochemistry. It would seem that mammaglobin immunohistochemistry could serve as a practical tool for confirming the diagnosis of MASC. In our evaluation of a diverse group of salivary gland neoplasms, we found that immunohistochemical detection of mammaglobin is consistently present in MASCs, but staining is also observed in other types of salivary gland neoplasms where it is unassociated with the *ETV6-NTRK3* rearrangement. Mammaglobin immunostaining was observed in 9 of 116 (8%) salivary gland tumors that did not harbor the *ETV6* rearrangement including 1 of 1(100%) low-grade cribriform cystadenocarcinoma, 2 of 3 (67%) polymorphous low-grade adenocarcinomas, 2 of 3 (67%) salivary duct carcinomas, 2 of 18 (11%) mucoepidermoid carcinomas, and 2 of 33 (6%) pleomorphic adenomas. In light of its suboptimal specificity, the diagnosis of MASC should not be based solely on the presence of mammaglobin staining. Instead, careful interpretation of mammaglobin staining together with the microscopic findings should resolve the differential diagnosis in most instances.

MASC is a generally well circumscribed proliferation of eosinophilic cells that have an apocrine appearance (Figure 1). Tumor nuclei are uniformly oval with open chromatin and a single nucleolus. At the architectural level, MASC characteristically grows as microcysts, macrocysts, and papillae. Pink secretory material is always encountered. MASC is regarded as a low-grade carcinoma, and high-grade microscopic features (e.g. high mitotic rate, tumor necrosis, highly infiltrative pattern of growth) are not well developed. The histologic features of MASC are very similar to those that may be encountered in acinic cell carcinoma. In the present study, all acinic cell carcinomas were mammaglobin negative, suggesting that the antibody is a valuable tool for differentiating those two entities. On the other hand, we found that mammaglobin may be positive in cases of pleomorphic adenoma, salivary duct carcinoma, mucoepidermoid carcinoma, polymorphous low-grade adenocarcinoma, and low-grade cribriform cystadenocarcinoma. Pleomorphic adenoma and salivary duct carcinoma are unlikely to be confused with MASC histologically. Pleomorphic adenoma is usually easily recognized by its chondromyxoidstroma and abundant myoepithelial cell component, and although salivary duct carcinoma does exhibit an apocrine appearance and a resemblance to breast carcinoma, it is a high-grade malignancy characterized by cellular pleomorphism and comedonecrosis (Figure 2A–B), features never encountered in MASC. Low-grade cystic forms of mucoepidermoid carcinoma have some architectural overlap with MASC, but at the cellular level, mucoepidermoid carcinoma is comprised of a mixed population of mucocytes, squamoid cells, and intermediate cells that is dissimilar to the monotonous appearance of MASC (Figure 2C–D). Polymorphous low-grade adenocarcinoma, like MASC, is composed isomorphic, bland cells. In addition, polymorphous low-grade adenocarcinoma is consistently S-100 positive like MASC. However, polymorphous low-grade adenocarcinoma is more variable architecturally; the cords and trabeculae that are common in polymorphous low-grade adenocarcinoma are not seen in MASC. Moreover, unlike MASC, polymorphous low-grade adenocarcinoma is highly infiltrative, and almost always demonstrates perineural invasion (Figure 2E–F).

Distinguishing MASC from low-grade cribriform cystadenocarcinoma (previously known as low grade salivary duct carcinoma) may be more problematic. The distinction is not trivial; while MASC may occasionally behave aggressively and even cause death, low-grade cribriform cystadenocarcinoma has not been known to recur or metastasize [21–23]. The one

case of low-grade cribriform cystadenocarcinoma available for this study was diffusely mammaglobin positive but negative for *ETV6* translocation (Figure 3). Low-grade cribriform cystadenocarcinoma was described before MASC was a recognized entity, and it is possible that some cases included in series of low-grade cribriform cystadenocarcinoma could actually be MASC. Indeed, the histologic features of the two tumors overlap. Both tumors may exhibit macrocystic spaces with papillae and surrounding areas of back-to-back ducts, apocrine appearing cells that may have vacuolated cytoplasm and lack pleomorphism, and diffuse S100 positivity [2–15, 21–23]. Low-grade cribriform cystadenocarcinoma has been described as being predominantly intraductal, but an intraductal tumor component has also been described in MASC [2, 7, 11]. Low-grade cribriform cystadenocarcinoma characteristically exhibits foci of gold to brown lipofuscin-like pigment, but may be difficult to distinguish from the hemosiderin that has been seen in MASC [2]. It is difficult to reach definitive conclusions with so few cases of low-grade cribriform cystadenocarcinoma tested for *ETV6* translocation (one in the current study, one by Skalova, et al. [1], and four by Chiosea et al. [7]), but a mammaglobin-positive tumor that exhibits a dominant intraductal cribriform component with slit-like spaces reminiscent of usual duct hyperplasia of the breast should raise the possibility of low-grade cribriform cystadenocarcinoma and probably prompt definitive genetic testing. Ultimately, a molecular reevaluation of low-grade cribriform cystadenocarcinoma is warranted to clarify its distinction from MASC.

Finally, although mammaglobin immunostaining is not limited to MASC, it could have other uses in diagnostic salivary gland pathology. Specifically, the utility of mammaglobin in the diagnosis of polymorphous low-grade adenocarcinoma deserves further study. The diagnosis of polymorphous low-grade adenocarcinoma is notoriously difficult in small biopsies, where it may be confused with pleomorphic adenoma and adenoid cystic carcinoma [24, 25]. We found that while 2 of 3 polymorophous low-grade adenocarcinomas were mammaglobin positive, only 6% of pleomorphic adenomas and none of the adenoid cystic carcinomas exhibited staining. This suggests a possible role for mammaglobin in differentiating polymorphous low-grade adenocarcinoma from its closest mimickers.

In summary, immunohistochemical expression of mammaglobin is consistently present in MASCs, but it is also observed in other types of salivary gland neoplasms that do not harbor the *ETV6* rearrangement. Suboptimal specificity of mammaglobin staining does not eliminate its use as a practical tool in the diagnosis of MASC. Mammoglobin staining is mostly observed in tumor types that do not routinely enter the differential diagnosis of MASC, but it is not observed in acinic cell carcinomas – the tumor most likely to be confused with MASC at the morphologic level. A diagnosis of MASC should not be made based solely on mammaglobin positivity, but strong mammaglobin staining is confirmatory for those tumors that exhibit classic MASC morphology even in the absence of testing for the*ETV6* rearrangement.

Acknowledgments

Funding: This work has been partially funded by the National Institute of Dental and Craniofacial Research (R01 DE013152-11).

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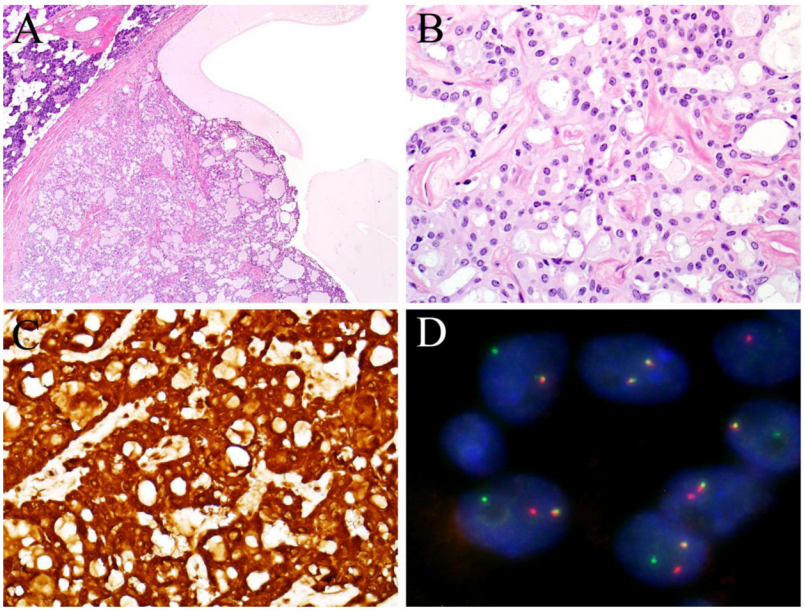

Figure 1.

Mammary analogue secretory carcinomas (MASCs) are usually circumscribed, and they frequently exhibit macrocystic and microcystic growth (A) (Hematoxylin and eosin, X40). MASC is comprised of a population of cells with abundant eosinophilic cytoplasm and uniform round to oval nuclei with open chromatin and a single nucleolus (B) (Hematoxylin and eosin, X400). All cases of MASC were strongly and diffusely positive for mammaglobin by immunohistochemistry (C) (Mammaglobin immunohistochemistry, X400). *ETV6* break apart FISH demonstrated one intact gene (i.e., orange and green together) and one rearranged *ETV6* gene (D).

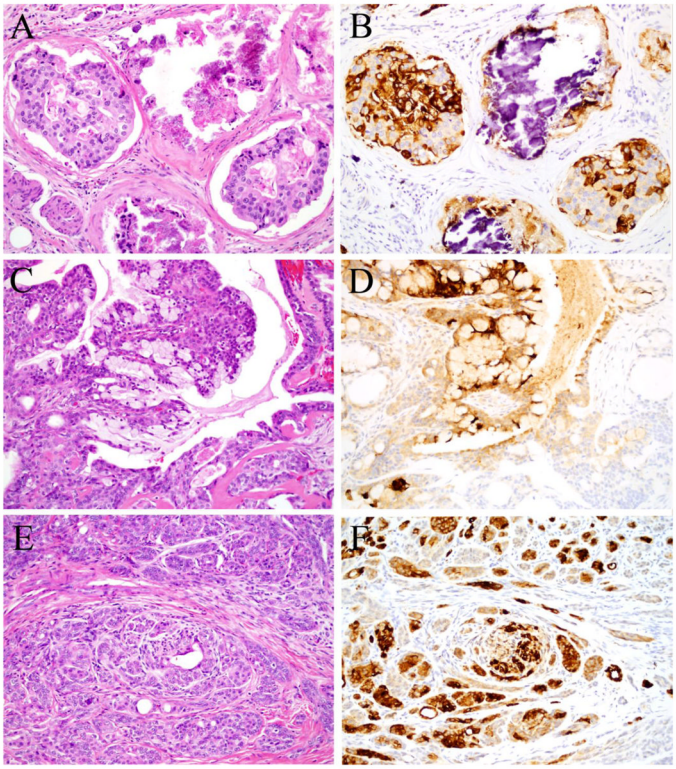

Figure 2.
Mammaglobin immunostaining was seen in cases of salivary duct carcinoma (A–B), mucoepidermoid carcinoma (C–D) and polymorphous low grade adenocarcinoma (E–F). However, in each case break apart FISH demonstrated two intact *ETV6* genes. (A, C, and E Hematoxylin and eosin; B, D, F, mammaglobin immunohistochemistry; all X200).

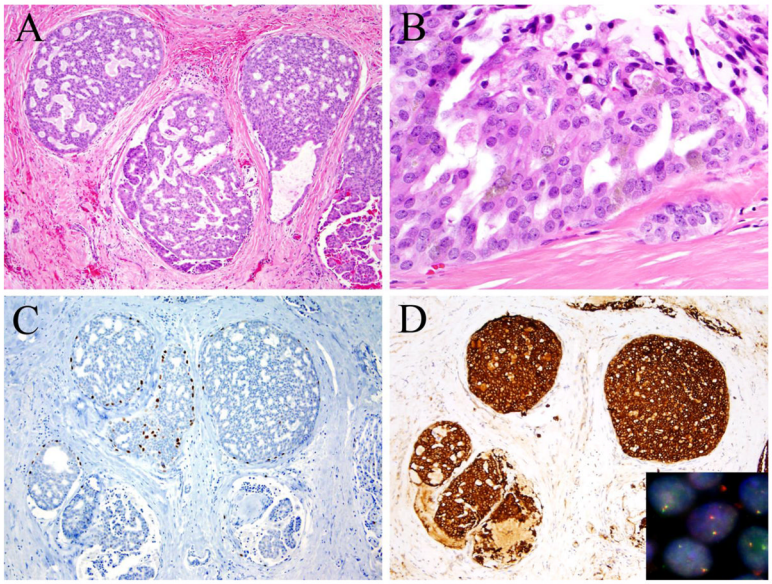

Figure 3.

Low grade cribriform cystadenocarcinoma exhibits cribriform growth with slit-like glandular spaces, reminiscent of usual duct hyperplasia of the breast (A) (Hematoxylin and eosin, X100). The cells of low grade cribriform cystadenocarcinoma are pink with monotonous round nuclei, similar to those of MASC. Golden-brown pigment may be seen in some tumor cells (B) (Hematoxylin and eosin, X400). Low grade cribriform cystadenocarcinoma usually has a predominantly intraductal growth pattern. The intact myoepithelial cell layer is highlighted by a p63 immunostain (C) (p63 immunohistochemistry, X100). This case of low grade cribriform cystadenocarcinoma was strongly positive for mammaglobin (D) (Mammaglobin immunohistochemistry, X100), but was negative for *ETV6* rearrangement by FISH (inset of D).

Table 1

Mammaglobin immunoreactivity in primary salivary gland neoplasms.

Diagnosis	Mammaglobin-positive cases/Total cases (%)	Comment
Mammary analogue secretory carcinoma	15/15 (100)	All strong and diffuse
Low grade cribriform cystadenocarcinoma	1/1 (100)	Diffuse and strong
Salivary duct carcinoma	2/3 (67)	Both strong and diffuse
Polymorphous low grade adenocarcinoma	2/3 (67)	Both strong, 1 diffuse and 1 focal
Mucoepidermoid carcinoma	2/18 (11)	Both strong and focal
Pleomorphic adenomas	2/33 (6)	1 diffuse and strong, 1 focal and weak
Acinic cell carcinoma	0/10 (0)	
Adenoid cystic carcinoma	0/44 (0)	
Adenocarcinoma, not otherwise specified	0/4 (0)	
Total	24/131 (18)	