Mucinous Myoepithelioma, a Recently Described New Myoepithelioma Variant

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Abstract Myoepithelial neoplasms are tumors composed almost exclusively of cells with myoepithelial differentiation. They frequently contain spindle, plasmacytoid or epithelioid shaped cells and may have oncocytic or clear cytoplasmic features. They are uncommon, accounting for 1.5 % of all salivary gland tumors and for 2.2–5.7 % of major and minor salivary gland tumors, respectively. Recently this author, together with several colleagues, have described three unusual myoepithelial tumors, two benign and one malignant that contained abundant intracellular mucin material, which they termed the mucinous variant of myoepithelioma. This represents a unique, previously undescribed subtype that does not fit in the current classification system. A literature review revealed several similar cases reported as “signet ring-cell” adenocarcinomas of salivary gland, which stained for myoepithelial markers, in addition to containing intracellular mucin material, that are more accurately classified as mucinous myoepithelioma. To date, there are 17 reported mucinous myoepitheliomas; four were classified as benign and 13 as malignant. Thirteen arose in minor salivary glands and four in the parotid gland. One patient presented with a lymph node metastasis. With minimal follow-up currently available, this appears to be a benign to low-grade malignancy.

Keywords Myoepithelioma · Myoepithelial · Salivary gland neoplasms · Oral cavity · Carcinoma · Mucin

Introduction

Myoepithelial neoplasms are uncommon, accounting for 1.5 % of all salivary gland tumors and for 2.2–5.7 % of major and minor salivary gland tumors, respectively [1]. Myoepithelioma is a benign salivary gland tumor composed of cells with myoepithelial differentiation that may be spindle shaped, plasmacytoid, or epithelioid in nature but also may occasionally have basaloid, oncocytic or clear cytoplasmic features [2, 3]. This tumor falls at one end of the spectrum of benign mixed tumor with only a few ducts allowed by most authors in this tumor category [2, 3]; a few authors, however, do not allow any ductal structures in a myoepithelioma and prefer to classify these latter tumors as myoepithelial predominant benign mixed tumors if any ducts are present [1, 3]. The stroma is frequently myxoid or hyalinized often with prominent basement membrane production; if cartilage or osteoid/bone is found, the tumor is best classified as a benign mixed tumor. In general, nuclear pleomorphism is minimal, but, as in mixed tumors, a mild to moderate degree of nuclear atypia with no associated increased mitotic or proliferative activity may be noted, particularly in those with oncocytic metaplasia. Malignant myoepithelioma, also known as myoepithelial carcinoma, is the malignant counterpart of benign myoepithelioma. A myoepithelial neoplasm is considered a myoepithelial carcinoma when it is composed almost exclusively of tumor cells with myoepithelial characteristics and, additionally, has a greater degree of pleomorphism, infiltrative growth, increased mitotic activity or neural invasion and the potential for metastasis [4].

Recently the author, together with several colleagues, encountered a subset of confirmed benign and malignant myoepithelial tumors containing intracellular mucin [5]. This represents a unique, previously unrecognized subtype

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of myoepithelioma that does not fit in the current classification systems. The three tumors all had abundant intracellular mucin and all three stained with at least one myoepithelial marker. Two were benign and one was malignant. The benign tumors arose in the parotid glands of 69 and 75 year old males. Tumor cells had abundant eosinophilic to foamy grayish-blue cytoplasm, often containing intracellular mucin, mild nuclear pleomorphism, fine peppery chromatin and inconspicuous nucleoli (Fig. 1). The first tumor stained for cytokeratin, smooth muscle actin (SMA), S-100 protein and glial fibrillary acidic protein (GFAP), while the second was positive for calponin, smooth muscle myosin heavy chain, p63, S-100 protein and CAM 5.2.

The malignant tumor arose in the hard palate of a 75 year old female. It was multinodular, focally invasive and was composed of nests and sheets of cells with moderate nuclear pleomorphism, prominent nucleoli with abundant lightly eosinophilic cytoplasm, a focally prominent plasmacytoid-type configuration and areas containing prominent intracytoplasmic

mucinous-type secretions with focal areas containing extracellular mucin material (Fig. 2). A tiny focus of bland ducts with hyalinized stroma was present adjacent to the tumor, raising the suspicion of it arising from a benign mixed tumor. It was positive for calponin, cytokeratin cocktail, S-100 protein, CK7, polyclonal carcinoembryonic antigen (focal) and GFAP.

A careful English literature review found 12 similar tumors, all published as signet ring carcinomas. Ghannoum and Freedman in 2004 [6] described seven malignant tumors of the minor salivary glands with cells containing mucin-filled vacuoles and eccentric crescent-shaped nuclei. The intracellular mucin was confirmed by PAS diastase and mucicarmine staining. By immunohistochemistry these tumors all showed positivity for CAM 5.2, SMA, S100 protein, HHF-35 and p63, and a subset also stained with GFAP. Singh et al. [7] reported a similar appearing carcinoma in the parotid gland in a 38 year old female. This tumor contained abundant intracellular mucin and, by

Fig. 1 Encapsulated parotid myoepithelioma in a 69 year old male. The tumor was composed of sheets of closely packed nests of plasmacytoid to polygonal cells with abundant eosinophilic to foamy grayish-blue cytoplasm, frequently containing intracellular mucin. It

was positive for intracellular mucin (mucicarmine stain, *lower left*), cytokeratin cocktail (*lower middle*) and S100 (*lower right*). It also stained for SMA and GFAP (not shown)

Fig. 2 Multinodular, focally invasive hard palate myoepithelial carcinoma composed of nests and sheets of cells with moderate nuclear pleomorphism and a focally prominent plasmacytoid-type configuration (*lower left*). Throughout much of the tumor were areas

with prominent intra-cytoplasmic mucinous-type secretions (*lower left* and *inset*) highlighted by alcian blue staining (*lower middle*). The calponin stain was diffusely positive (*lower right*)

immunohistochemistry, tumor cells had prominent peripheral staining with cytokeratin cocktail and focal peripheral staining with SMA. Bastaki and Summersgill [8] reported an 18 year old African American male with a tumor in the left buccal mucosa/mandibular buccal vestibule region. A mucicarmine stain highlighted intracellular and stromal mucin and tumor cells were strongly positive for cytokeratins and p63. Recently Bastaki et al. [9] presented, in abstract form, a series of four signet ring carcinomas, which also included the latter previously published case. Their tumors uniformly had a signet ring appearance embedded in a myxoid stroma with intracellular mucin confirmed by mucicarmine and PAS diastase staining in all cases. They all stained for cytokeratins. One case was positive for calponin and p63, a second case stained for calponin, p63 and S100 protein, the third case was positive for p63 (previous published case by same author [8]); their fourth case was negative for these myoepithelial markers.

In addition to the above cases, there were two previously published similar appearing benign tumors with abundant

intracellular mucin and areas of plasmacytoid differentiation, but without documented myoepithelial characteristics. The first was a benign tumor arising in a 21 year-old male with an upper lip mass [10]. It contained numerous bland, mucin containing signet ring cells that stained with keratin AE1/AE3. This case was recently presented by M. Michal at the European Society of Pathology meeting in Prague, September 2012, as part of a head and neck slide seminar; illustrations were included in the conference CD. The photos of this case illustrated numerous bland signet ring cells but, in addition, many typical plasmacytoid cells with eccentric nuclei and abundant eosinophilic cytoplasm were intermixed with the signet ring cells. The second case was described by Foschini et al. [11] in a 31 year old female. This tumor arose in the lip, had prominent signet-ring cell morphology and exhibited benign behavior (Fig. 3). It was composed mainly of cells with a large intracytoplasmic vacuole containing mucin, confirmed by alcian blue and mucicarmine (Fig. 3, lower right) staining. In areas, plasmacytoid cells with eccentric nuclei and abundant eosinophilic cytoplasm were

Fig. 3 Encapsulated benign tumor with signet ring type cells arising in the lip of a 31 year old female [11]. There are numerous plasmacytoid type cells (see periphery of *upper right* and *lower left*

figures) as well as mucin containing cells (*lower right*, mucicarmine stain) with signet ring morphology (*upper right* and *lower left*). Case material kindly supplied by Dr. Maria Pia Foschini

intermixed with the signet ring cells. This case was histologically similar to the other cases, but did not stain with myoepithelial markers: Cytokeratin 7 and antimitochondrial antibody were strongly positive in the tumor cells; however, p63, CK4 and SMA were negative. In addition this tumor did not stain with other myoepithelial markers (calponin, HHF35, smooth muscle myosin heavy chain and glial fibrillary acidic protein; personal communication). As plasmacytoid myoepitheliomas are known to occasionally not stain with myoepithelial markers [12; personal experience], it is likely that these two tumors are also mucinous myoepitheliomas.

To date, there are 17 mucinous myoepitheliomas reported; 13 arose in minor salivary glands, most frequently the palate and four in the parotid gland; the male to female ratio is approximately equal. Four have been classified as benign, and 13 as malignant neoplasms. One patient presented with a lymph node metastasis. Tumors ranged in size from 1 to 5 cm and all were treated by

surgical excision. Follow-up information was available in only 5 patients, ranging from 5 months to 8 years; all are alive and well. To date, this appears to be a benign to low-grade malignancy. However more experience with this unusual tumor is necessary to better understand its biologic behavior. One should use the same histologic criteria for this tumor to evaluate for malignancy as any other myoepithelioma, i.e. encapsulation, circumscription, destructive peripheral growth, mitotic and proliferative rates, perior intraneural invasion, tumor necrosis and degree of pleomorphism.

The main differential diagnostic consideration for this myoepithelioma variant is with other mucin producing carcinomas that may contain signet ring cells, including colloid carcinoma, mucoepidermoid carcinoma, mucinous cystadenocarcinoma and salivary duct carcinoma. Colloid carcinoma has large pools of mucin in which there are small aggregates of tumor cells, which are not seen in mucinous myoepitheliomas and myoepithelial markers are

negative. Mucoepidermoid carcinoma may also contain signet ring cells, however, myoepithelial markers are absent and thorough histological sampling, will reveal areas more typical of mucoepidermoid carcinoma with squamous, intermediate, and mucin-secreting columnar epithelium. Mucinous cystadenocarcinoma also may have focal areas with signet ring cells. These are typically more cystic and papillary than mucinous myoepithelioma, do not stain with myoepithelial markers and, unlike mucinous myoepithelioma, have mucin containing cuboidal or columnar cells lining many of the cystic spaces and papillary fronds. Salivary duct carcinoma may also contain signet ring cells. These tumors do not stain with myoepithelial markers and with careful histological sampling, will contain areas with the histological appearance of a typical “breast ductal carcinoma”.

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