Oncocytic and Apocrine Epithelial Myoepithelial Carcinoma: Novel Variants of a Challenging Tumor

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Abstract Epithelial myoepithelial carcinoma (EMCa) is a rare but well characterized biphasic salivary gland malignancy with several variant morphologies. Oncocytic and apocrine EMCa are uncommon variants that constitute up to 8 % of all EMCa. Both variants invoke an eosinophilic or oncocytic differential diagnosis and challenge the traditional requirement of clear myoepithelial cells for EMCa. Oncocytic EMCa occurs in patients a decade older than conventional EMCa. This variant is often papillary with calcification and associated with sebaceous components and occurs in older individuals. Apocrine EMCa is named for its apocrine ductal component, which may be mistaken for salivary duct carcinoma. In this variant, the epithelial component often shows overgrowth in a cribriform or even solid pattern and is immunophenotypically defined by androgen receptor and gross cystic disease fluid protein 15 positivity. The most important aspect of differentiating both oncocytic and apocrine EMCa from other salivary oncocytic tumors is recognition of the biphasic nature of these variants and confirmation that the abluminal outer layer consists of plump, ‘activated’ myoepithelial cells, regardless of tinctorial characteristics. Both oncocytic and apocrine EMCa behave very indolently in the limited literature to date.

Keywords Epithelial-myoepithelial carcinoma · Oncocytic · Apocrine · Sebaceous · Salivary gland

Introduction

Epithelial myoepithelial carcinoma (EMCa) is a rare salivary gland malignancy that comprises about 1–2 % of all salivary gland tumors and 2–5 % of malignant salivary gland tumors [1–3]. Initially described by Donath et al. in 1972 [4], EMCa was likely recognized as early as 1956 and reported under a variety of names such as adenomyoepithelioma, clear cell adenoma, tubular solid adenoma, monomorphic clear cell tumor, glycogen-rich adenoma, glycogen-rich adenocarcinoma, clear cell carcinoma [1, 3, 5–8]. EMCa is typically occurs in the 6th and 7th decades of life with a slight female predilection. This tumor can occur at essentially any site with salivary or mucoserous glands, including the lower respiratory tract, but has a predilection for major salivary gland with 60–75 % occurring in the parotid gland [1–3, 9, 10]. The typical presentation for EMCa is fairly non-descript; usually as a slow growing painless mass that is on average about 3 cm on presentation [1, 3]. Overall, EMCa behave as low grade malignancies that recur in about one-third to one half of patients, though the time to recurrence is often a decade after initial presentation [2, 11, 12]. While earlier series report up to 40 % patients dying from disease and distant metastases in 25 % [11, 12], more recently, the 5 and 10 year survival for EMCa has been reported 94 and 82 % respectively with only a 2 % rate of distant metastasis, likely secondary to improved initial surgical management.

General Histologic and Immunophenotypic Features

EMCa is the prototypical ‘biphasic’ salivary gland tumor composed of a tubular to nested bilayered arrangement of inner (luminal) ductal cells, and outer (abluminal) myoepithelial

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cells. EMCa invades in a deceptively innocuous fashion with a multinodular pushing (rather than frankly infiltrative) border (Fig. 1a) and tumor nests are accompanied by varying degrees of hyaline sclerosis [1, 3]. About 25–30 % show at least partial encapsulation [2]. The ductal component is typically comprised of small lightly eosinophilic cuboidal cells forming tubules with the caliber of intercalated ducts (the presumed site of origin for this tumor). Classically, myoepithelial component consists of larger polygonal cells with clear cytoplasm (Fig. 1b). This myoepithelial cell population usually predominates in a 2:1 ratio and in some cases shows overgrowth and compresses the ductal component to the extent that it is barely discernible by light microscopy [1, 2]. Cystic change and bilayered papillary growth patterns can be seen in about 10 % of cases [2]. The vast majority of EMCa have low grade cytomorphic features, but up to one-third may show perineural invasion [2]. Angiolymphatic invasion and necrosis, which appear to correlate with local recurrence, are less frequent [2].

Immunohistochemical staining can be used to highlight the biphasic appearance of EMCa. The luminal ductal components are strongly positive for cytokeratins using either pankeratin cocktails, or lower molecular weight keratins (Fig. 2a). The myoepithelial cells are typically positive for p63, and muscle markers such as smooth muscle actin, calponin, and smooth muscle myosin heavy chain as well as vimentin (Fig. 2b, c). This outer myoepithelial cell layer may be positive when stained with cytokeratin cocktails or even low molecular weight cytokeratins, but with a lower intensity in comparison to the ductal component. In contrast, while high molecular weight cytokeratins are typically negative in the ductal component they are frequently positive in the abluminal myoepithelial cells. In addition, though not specific for myoepithelial lineage, vimentin is almost invariably positive in the myoepithelial cells. S100 protein, while classically used as a myoepithelial marker in EMCa, has been shown to have variable staining, and does not show much fidelity to this

lineage since it often stains the ductal component as well (Fig. 2d). GFAP may show occasional staining in the myoepithelial component [1–3]. Ki-67 is typically less than 20 %. Bcl-2 and C-kit are often positive, the latter in the ductal component only. Strong p53 immunoreactivity is very uncommon [2].

Variant Morphology in General

EMCa, though rare, has several described variants which result from various combinations of unusual growth patterns, ‘heterologous’ elements, nuclear features, and/or cytoplasmic tinctorial characteristics. These include EMCa with high grade transformation, EMCa ex pleomorphic adenoma, double clear EMCa, sebaceous EMCa, oncocytic EMCa, and apocrine EMCa. Aside from these named variants, the myoepithelial cells in EMCa may show alterations such as ‘ancient change’ or spindled morphology with Verocay like palisading or squamous metaplasia (Fig. 3a) [2, 13–15]. The oncocytic and apocrine variants are the main focus of this review, but two important variants are summarized here.

EMCa with high grade transformation encompasses tumors designated historically as dedifferentiated EMCa (Fig. 3b) and EMCa with anaplasia, but also depicts progression to undifferentiated carcinoma without a discernible lineage [2, 15]. In one series, these comprised about 7 % of all EMCa [2]. The mean patient age at presentation is 72 years, about one decade later than that of conventional EMCa [16]. Unlike adenoid cystic carcinoma with high grade transformation, which is invariably a transformation showing a ductal phenotype [17], EMCa with high grade transformation can demonstrate progression in either or even both components [15]. While follow-up is limited on such cases, this variant appears to be more aggressive than classic EMCa. As such the therapeutic ramifications of this variant include more aggressive surgical management

Fig. 1 Classic EMCa. **a** Typical nodular growth pattern (Hematoxylin and Eosin (H&E), $\times 20$ magnification). **b** Classic biphasic tubular appearance consisting of an inner ductal layer of cuboidal epithelium

with pale eosinophilic cytoplasm and an outer layer of large polygonal clear myoepithelial cells (H&E, $\times 100$)

Fig. 2 Basic immunoprofile for EMCa. **a** Cytokeratin AE1/3 highlights inner ductal cells with weaker staining in the outer myoepithelial cells (2'-diaminobenzidine chromogen (DAB), $\times 200$). **b** Smooth muscle actin and **c** p63 highlights the outer myoepithelial

cells (DAB both $\times 200$). **d** S100 protein is not reliable as a myoepithelial marker as it is staining the ductal component more prominently. In the center is a nerve as internal control (Alkaline phosphatase red chromogen, $\times 200$)

Fig. 3 Sample variant morphologies in EMCa. **a** Squamous metaplasia in EMCa (H&E, $\times 100$). **b** EMCa with high grade transformation. On the left the tumor shows a bilayered appearance of typical

EMCa, but then progresses to a solid pleomorphic overgrowth of ductal cells (H&E, $\times 200$)

with radiotherapy and perhaps neck dissection, in contrast to the usual EMCa [15, 16]. Recognizing that EMCa with high grade transformation is a high grade carcinoma is not particularly challenging, but the transformed component itself does not usually have a distinctive morphology. The key to recognizing that the carcinoma is a transformation of EMCa (rather than another high grade carcinoma type) is identification of a more classic appearing area of EMCa and documentation of a bilayered, biphasic phenotype in such an area [2, 15].

Another relevant 'variant' noted for having a precursor lesion is EMCa arising from a pleomorphic adenoma. About 2 % of EMCa arise from pleomorphic adenoma [2]. Conversely, EMCa ex pleomorphic adenoma comprise only 1 % of all carcinomas ex pleomorphic adenoma [18]. The importance of this variant is the diagnostic challenge it poses in distinction from a mere cellular component of a pleomorphic adenoma since both considerations are biphasic. Useful clues for distinction of an EMCa component are the presence of extension beyond the tumor

Fig. 4 Oncocytic EMCa. **a** Classic EMCa, *left*, with small caliber ductal components transitioning to oncocytic EMCa, *right*, with larger caliber tubules and ducts (H&E, $\times 100$). **b** Ductal component is columnar and densely oncocytic while the outer myoepithelial layer is still somewhat clear (H&E, $\times 200$). **c** When the myoepithelial cell

layer is also oncocytic as seen here, the biphasic nature is difficult to appreciate at lower magnification (H&E, $\times 200$). **d** Close examination will allow delineation of a bilayer (H&E, $\times 600$). **d** Bilayered papillary growth (H&E $\times 100$). **e** Sebaceous differentiation in oncocytic EMCa (H&E, $\times 200$)

capsule, sclerosis rather than a cellular myxoid stroma, and a larger more polygonal appearance to the myoepithelial component in EMCa. Limited evidence to date suggests that EMCa ex pleomorphic adenoma have a similar behavior to EMCa de novo.

Oncocytic and Apocrine EMCa

Oncocytic and apocrine EMCa are perhaps the most common variants of EMCa. Oncocytic EMCa was described initially by Savera and Salama in 2005 [19] while apocrine EMCa was described by Seethala et al. [13]. While oncocytic and apocrine changes may be seen focally

in many otherwise conventional EMCa, oncocytic and apocrine EMCa are generally only designated as variants when the oncocytic or apocrine components comprise greater than 50 % of the tumor area. Lesions defined in this way characterize roughly 8 % of all EMCa in one institutional experience [2, 13]. The demographic profile of oncocytic and apocrine EMCa are similar to classic EMCa with one notable exception: the mean age of patients with oncocytic EMCa is about a decade later. Thus similar to other oncocytic lesions, oncocytic EMCa likely reflects a senescent phenotype. Both variants are unique in that they are ‘pink’ or oncocytoid in appearance challenging the classical requirement for clear cell morphology in the myoepithelial component of EMCa.

Fig. 5 Apocrine EMCa. **a** Classic EMCa, *left*, with small caliber ductal components and scant cuboidal epithelium transitioning to apocrine EMCa, *right*, with large caliber ducts with large eosinophilic ductal cells showing prominent decapitation secretions (H&E, $\times 200$).

Ductal overgrowth in **b** cribriform and **c** solid patterns is common (H&E, $\times 200$). **d** Apocrine ductal elements often show profound nuclear pleomorphism (H&E, $\times 200$)

Like classic EMCa, oncocytic EMCa consists of a bilayered arrangement of tubules with inner ductal cells and abluminal myoepithelial cells. However, the tubules are larger in caliber, more akin to striated ducts than intercalated ducts. Of interest, is the exceptionally rare variant ‘double clear’ EMCa, in which both the ductal and myoepithelial component show clear cytoplasm, and is the exact opposite of oncocytic EMCa, although both have a similar tubule caliber. The ductal component in oncocytic EMCa consists of cuboidal to columnar oncocytic cells with granular cytoplasm, again reminiscent of striated duct epithelium. The outer myoepithelial cell layer varies and ranges from clear to oncocytic (Fig. 4a, b). Nuclei of the myoepithelial component are larger and more vesicular than the ductal component, similar to classic EMCa. When the myoepithelial component is oncocytic, the bilayered appearance may be difficult to discern (Fig. 4c, d). Aside from this basic appearance, oncocytic EMCa has a propensity to show a bilayered papillary growth pattern (Fig. 4e) and luminal calcifications. Additionally, almost all oncocytic EMCa also show sebaceous differentiation (Fig. 4f), hence the earlier descriptor of ‘oncocytic-sebaceous’ EMCa [2]. However, it has been noted that purely sebaceous EMCa exist [14], and anecdotally, oncocytic EMCa without sebaceous differentiation have been noted.

The sebaceous elements vary, ranging from solid nests interspersed within myoepithelial rich areas to small intraductal proliferations transitioning from the oncocytic ductal epithelium. This variant can show perineural and angiolymphatic invasion and invades in a multinodular fashion similar to classic EMCa. Follow up on reported cases is limited, but it appears that oncocytic EMCa has an indolent behavior in keeping with a low grade tumor type [2, 13].

Apocrine EMCa is similar morphologically to oncocytic EMCa on a superficial level. However, closer examination reveals subtle differences. In apocrine EMCa, the ductal component is distinctive; while eosinophilic, the apocrine ductal component is definitionally highly secretory and shows decapitation secretions or apical snouts in the lumina of tubules (Fig. 5a) in sharp contrast to the smooth luminal surface of oncocytic EMCa. Additionally, the ductal component in apocrine EMCa has somewhat of a propensity for overgrowth, either in a solid or cribriform fashion (Fig. 5b, c). Even in more solid areas, apocrine EMCa have more secretory vacuoles than oncocytic EMCa. Finally, the nuclei of the ductal component in apocrine EMCa are often large (larger than the myoepithelial cell nuclei), anisomorphic, and vesicular with prominent nucleoli (Fig. 5d). The myoepithelial components of an apocrine EMCa are less

Fig. 6 Immunohistochemical and ultrastructural features in oncocytic and apocrine EMCa. **a** Oncocytic EMCa mitochondria can be highlighted by strong phosphotungstic acid-hematoxylin positivity ($\times 400$). **b** Similarly, anti-mitochondrial antibody is also positive. Striated duct internal control on right (DAB, $\times 200$). Apocrine EMCa shows ductal elements that are **c** Androgen receptor positive, and

d GCDFP-15 positive (both DAB, $\times 200$). **e** Ultrastructurally, oncocytic EMCa shows abundant mitochondria (mi, *inset*) in the ductal cells (*arrow*) in comparison to the myoepithelial cells (*asterisk*) invested by a thick basement membrane (bm), (original magnification $\times 2,650$, inset magnification $\times 66,000$). **f** Sebaceous elements may be highlighted on frozen section using oil red O ($\times 100$)

frequently oncocytic and often clear, similar to classic EMCa. Unlike oncocytic EMCa, apocrine EMCa have not been seen in association with sebaceous elements, and do not seem to show papillary growth patterns and calcifications as frequently. Apocrine EMCa also appears to have an indolent course [13]. Interestingly, rare hybrid tumors of EMCa and salivary duct carcinoma have been described, and it is plausible that apocrine EMCa is an ‘intermediary’ or ‘bridge’ form to such a hybrid carcinoma [20].

Immunohistochemical features for both oncocytic and apocrine EMCa are similar to classic EMCa in that the ductal components of both variants are also strongly positive for pankeratins or low molecular weight keratins,

while the myoepithelial components can be highlighted with p63, muscle markers and vimentin [2, 13]. Additionally, the ductal component of oncocytic EMCa is strongly phosphotungstic acid hematoxylin positive and positive for antimitochondrial antibody (Fig. 6a, b). The ductal component of apocrine EMCa is also androgen receptor and gross cystic disease fluid protein-15 positive (Fig. 6c, d), and often Her-2/neu positive. Ultrastructurally, as with most oncocytic lesions, the ductal cells in oncocytic EMCa demonstrate abundant, often abnormal appearing mitochondria (Fig. 6e). Apocrine EMCa ductal cells on the other hand will show numerous intracytoplasmic vacuoles and few mitochondria [13]. The sebaceous elements in

Fig. 7 A tree algorithmic approach to select oncocytic and eosinophilic salivary gland tumors. *AMA* antimitochondrial antibody, *ApEMCa* apocrine epithelial-myoepithelial carcinoma, *AR* androgen receptor, *CA* carcinoma, *GCDFP-15* gross cystic disease fluid protein 15, *H2N* HER2/

neu, *NOS* not otherwise specified, *OEMCa* oncocytic-sebaceous epithelial-myoepithelial carcinoma, *PA* pleomorphic adenoma, *PTAH* phosphotungstic acid hematoxylin. Reprinted from Seethala et al. [13]. Permission granted by the Archives of Pathology and Laboratory Medicine

oncocytic EMCa are often p63 and keratin positive while negative for actin and other muscle markers. Interestingly, unlike cutaneous sebaceous lesions, sebaceous elements in EMCa appear to be androgen receptor negative [2, 13]. However, markers such as adipophilin and perilipin are still positive [14], and on frozen tissue, oil red O stains may highlight intracytoplasmic lipid vacuoles (Fig. 6f).

Unlike classic EMCa, oncocytic and apocrine EMCa invoke an oncocytic/eosinophilic tumor differential diagnosis. For oncocytic EMCa, the major challenge is to distinguish this variant from benign entities such as oncocytoma, oncocytic cystadenoma, Warthin tumor or nodular oncocytic hyperplasia. On the other hand, apocrine EMCa must be distinguished from the more aggressive salivary duct carcinoma and salivary duct carcinoma in situ.

Resolving the diagnosis can be done with an algorithmic approach highlighted in Fig. 7. The critical step in the decision making tree is, of course, recognition of the biphasic nature of either of these variants. To this end it must be noted that p63 is positive in the periphery of tumor nests in oncocytoma, but not in a distinctly bilayered

fashion as seen in oncocytic EMCa. Also for salivary duct carcinoma in situ, there is an outer p63 positive delimiting layer that represents the residual normal basal layer of the involved duct rather than the actual neoplasm.

Once the biphasic nature of a tumor is established, confirmation that the outer abluminal cell layer is myoepithelial is the key to distinguishing oncocytic and apocrine EMCa from Warthin tumor and oncocytic cystadenoma, which though bilayered, have a peripheral layer that is phenotypically basal rather than myoepithelial (only p63, CK 5/6 positive, but muscle marker negative). Additionally, unlike the outer layer of Warthin tumor and cystadenoma, the myoepithelial cells of these EMCa variants are larger and more polygonal (i.e., a more 'activated' appearance).

The remaining entities in the differential diagnosis once the myoepithelial nature of the outer cell layer in oncocytic and apocrine EMCa is established, include sclerosing polycystic adenosis, pleomorphic adenomas (PA) with oncocytic/apocrine change or salivary duct carcinoma arising in PA. Distinction here can be subtle and challenging. Unlike EMCa, sclerosing polycystic adenosis has

attenuated myoepithelial components. Pleomorphic adenomas, though biphasic and remarkably similar in appearance to EMCA in more cellular areas, are not usually multinodular and permeative, and should have chondromyxoid stroma. In pleomorphic adenomas, the myoepithelial elements blend into this stroma, while in EMCA, the myoepithelial cell layer is distinct from the stroma, and is in fact often delineated by a prominent basement membrane.

Summary

Although EMCa is rare overall, oncocytic and apocrine EMCa are reasonably common variants and challenge the dogma that a clear cell outer myoepithelial component is required for the diagnosis of EMCa. Oncocytic EMCa is often associated with sebaceous components and occurs in older individuals. Apocrine EMCa is named for its apocrine ductal component, which may be mistaken for salivary duct carcinoma. Both variants have a favorable outcome to date. The differential diagnosis for these variants encompasses several oncocytic or eosinophilic ‘pink’ tumors of the salivary gland, but keys to distinction include recognition of biphasic growth in oncocytic and apocrine EMCa.

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