



Squamoglandular Variant of Acinic Cell Carcinoma: A Case Report of a Novel Variant

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Abstract

While salivary gland tumors have considerable plasticity, juxtaposition of the morphologies of two named tumor types is rare. Tumors with both mucoepidermoid and serous acinar components, dubbed “mucoacinar” carcinomas were recently characterized, and based on morphologic and molecular features, considered variants of mucoepidermoid carcinoma. Here we describe a unique case of a 59-year-old male with a 0.9 cm right parotid mass with a similar blend of mucoepidermoid-like and acinar elements that instead has a molecular phenotype of acinic cell carcinoma, essentially the reverse of mucoacinar carcinoma. The tumor was fairly well circumscribed with a prominent tumor associated lymphoid response. It consisted of a predominant bland but basaloid squamoid proliferation with scattered pockets of serous acinar differentiation as well as rare mucous cells and tubules. The tumor showed diffuse cytokeratin and DOG1 reactivity as well as p40 expression in the squamoid components. Immunostaining for NR4A3 was diffusely positive, and an *NR4A3* rearrangement was noted on fluorescence in situ hybridization, while testing for *MAML2* and *MSANTD3* rearrangements were negative. Based on these findings, this tumor is best considered a “squamoglandular variant of acinic cell carcinoma.” Morphologic and clinical evidence argues against this representing a form of high-grade transformation. While overall bland, the differential diagnosis may include various basaloid tumors in the parotid gland, both primary and metastatic.

Keywords Carcinoma, Mucoepidermoid · Acinic cell carcinoma · Nuclear receptor subfamily 4, Group A, Member 3 · Hybridization in situ, fluorescence · Molecular diagnostic techniques · Phenotype

Introduction

Acinic cell carcinoma (AciCC) was described as early as 1892 by Nasse [1]. Initially described as adenoma, it was only about 6 decades later that its malignant potential was recognized [2, 3]. Since then AciCC has been regarded as a low-grade malignant salivary gland neoplasm that has a preponderance for the parotid gland [4]. The histologic hallmark of these tumors is the presence of serous acinar differentiation which can be either focal or diffuse. In addition to this integral feature, AciCC also may have various mixtures

of intercalated, vacuolated, clear and non-specific glandular components arrayed in a mixture of solid, microcystic, papillary-cystic and follicular patterns [5].

Aside from this morphologic spectrum, the phenomenon of high-grade transformation (HGT), historically known as dedifferentiation [6–8], is not uncommon (~10–15%) [9] in AciCC, resulting in progression to a pleomorphic aggressive high grade non-specific ductal type carcinoma. At least one case of AciCC with sarcomatoid transformation has been described as well [10]. In general, the diagnosis of AciCC-HGT are still requires confirmation of serous acinar differentiation. Interestingly enough, acinar differentiation, while a defining feature of AciCC, is not restricted to this category. Sclerosing polycystic adenoma (previously known as sclerosing polycystic adenosis) is a neoplastic apocrine ductal lesion with a characteristic acinar component with distinctive coarse red zymogen granules [11]. Additionally, a recently described variant of mucoepidermoid carcinoma (MEC), “mucoacinar” carcinoma (MAC) contains a mixture of typical MEC as well as a serous acinar component

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[12]. Justification for placement as a variant of MEC rather than AciCC was based on the small proportion of overall tumor comprised by the acinar component, and molecular confirmation of *CRTC1-MAML2* fusions which are characteristic of MEC. Furthermore, a survey of *MSANTD3* [13] and *NR4A3* rearrangements [14], recently described in AciCC with the latter arguably being defining, was negative in these MAC. However, we have now encountered a tumor that shows similar mixture of squamoglandular and acinar components, but counter to what has been described so far in MAC, we document for the first time a case with phenotypic and molecular features of AciCC.

Case Report

Clinical Features

The patient is a 59-year-old male with a 0.9 cm partially cystic right anterior parotid mass. The excision of this mass and concurrent completion superficial parotidectomy were received in-consultation. No other relevant history was noted.

Microscopic Examination

On low power microscopic examination, the tumor consisted of a predominantly solid well-demarcated mass with central cystic change and a prominent tumor associated lymphoid response (Fig. 1A). The majority of tumor cells had a squamoid appearance with tumor cells ranging from somewhat basaloid with scant cytoplasm to more epidermoid with somewhat eosinophilic cytoplasm (Fig. 1B). The cells were arranged predominantly in a solid, streaming pattern. Additionally, minor ductal and acinar components were interspersed throughout the tumor (Fig. 1C, D), comprising only ~ 20% of the tumor surface area, and rare mucous cells were noted as well.

No perineural or angiolymphatic invasion were noted. Also notably, no features of high-grade transformation, (i.e. anaplasia, mitoses, necrosis) were identified. The completion superficial parotidectomy showed no tumor, and three benign intra/periparotid lymph nodes.

Ancillary Studies

Serous acinar differentiation was highlighted by granular positivity with PAS after diastase treatment, while a mucicarmine highlighted the focal mucous components (Fig. 2A). On immunohistochemical analysis (see Table 1), the majority of tumor cells with the exception of the ductoacinar elements were p40 positive (Fig. 2B). On the other hand, all components were positive for CK7, CAM 5.2, DOG-1

(Fig. 2C) and NR4A3 (Fig. 2D). SOX-10 (Fig. 2E) was only positive in rare ductal elements. Other stains: S-100, smooth muscle actin, synaptophysin and p16 were negative. Fluorescence in-situ hybridization (FISH) for *MAML2* performed at a reference laboratory (Unpublished method; <https://www.mayocliniclabs.com/test-catalog/Performance/58105>) was negative. Fluorescence in situ hybridization for *MSANTD3* and *NR4A3* rearrangements was performed as previously described [12]. The tumor was positive for *NR4A3* rearrangements (Fig. 2F) and negative for *MSANTD3* rearrangements.

Treatment/Follow-Up

Given the juxtaposition of acinar and squamoglandular differentiation with an acinar predominant immunoprofile and molecular phenotype, this tumor was considered a squamoglandular variant of acinic cell carcinoma. The patient had limited follow-up available (less than 4 weeks) without significant events.

Discussion

With the recent expansion of defining molecular alterations in salivary gland tumors, previously unclassifiable tumors have become increasingly definable, either pushed into existing categories or populating a new category altogether. Furthermore, tumors with characteristics of two tumor types as seen here can more accurately defined.

Scenarios for this occurrence may either represent “collision tumors,” tumors with “divergent” or “heterologous” differentiation, or true “hybrid tumors.” A collision between two topographically related distinct salivary primary tumors is predicted to be exceptionally rare given that multiple ipsilateral synchronous primaries are rare to begin with, comprising ~ 0.4% of salivary gland tumors [15]. Hybrid tumors are also reportedly rare, and constitute < 0.1–0.4% of salivary tumors [16, 17]. However, separation of a hybrid tumor from a tumor with divergent differentiation towards another tumor type is not well delineated. The initial definition by Seifert and Donath [16] for hybrid tumor was simply a tumor with two different tumor morphologies each of which conform to the exactly defined corresponding tumor category yet share a topographical area. We now know that most tumors that seem to fulfill this definition actually share a clonal origin and the molecular characteristics of one base tumor type, with the secondary morphology representing a form of morphologic mimicry. Such tumors in our opinion are more aptly designated as variants of the base tumor with divergent differentiation or in some cases, simply HGT [18–22]. When reserving the definition of “hybrid tumor” for tumors that are biphenotypic both from a morphologic

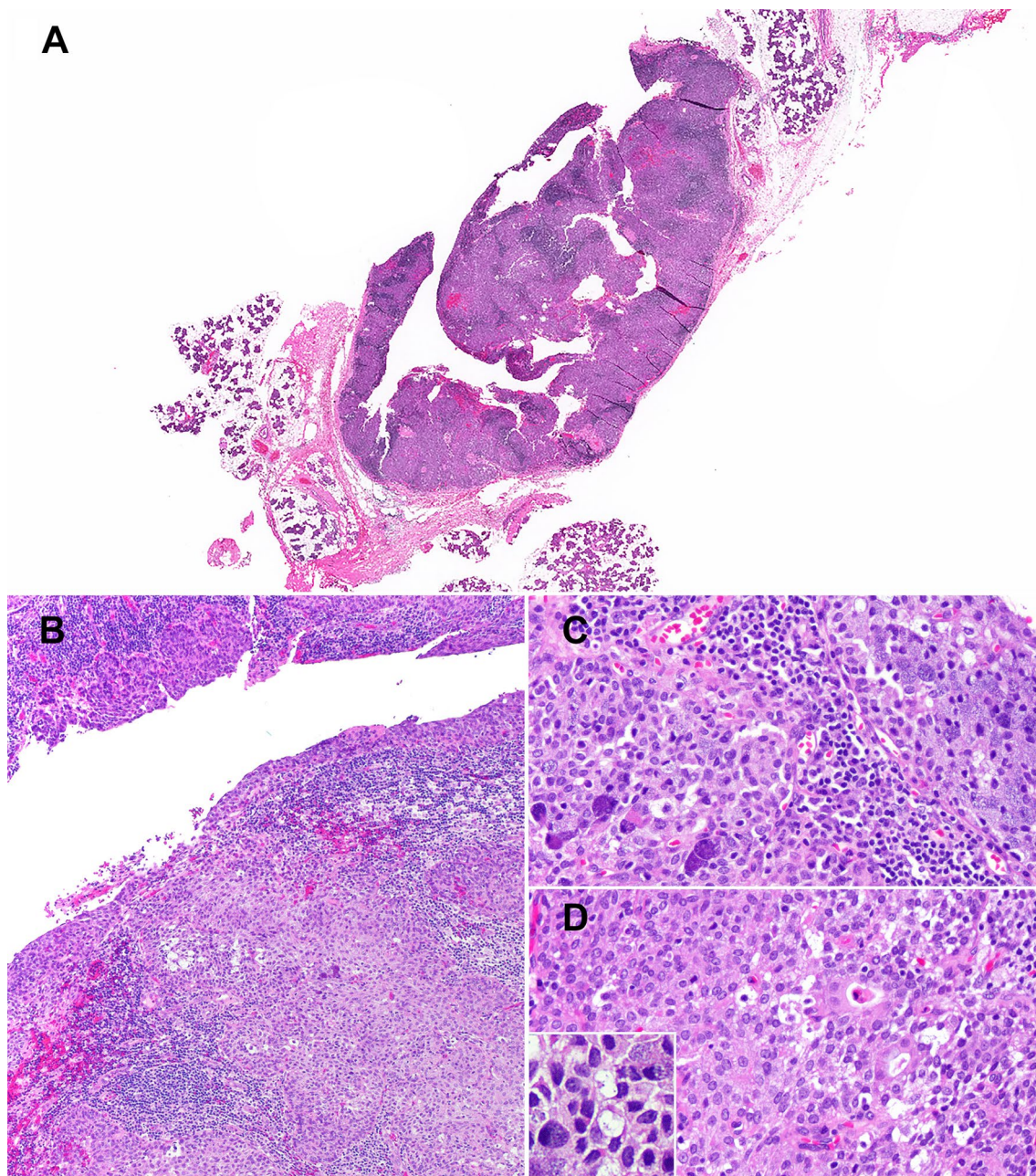


Fig. 1 Morphologic features of case. **A** This somewhat basaloid parotid tumor was fairly well circumscribed with a prominent tumor associated lymphoid proliferation and central cystic change (H&E, 0.4×). **B** The cystic lining and solid nests within are composed of

basophilic to lightly eosinophilic uniform squamoid cells (H&E, 4×). **C** Acinar (H&E, 20×), and **D** non-specific ductal (H&E, 20×) elements are a minor but significant component of the tumor. Inset (H&E, 20×) rare mucous cells are noted

and molecular standpoint, it would then follow that true salivary hybrid tumors are even rarer than reported [12].

Interestingly, morphologic coexistence of MEC and AciCC elements was initially described in what did appear to represent a collision process by Ballestin et al. [23]. Bundele et al [12] subsequently described 11 cases of MAC, also showing shared MEC and AciCC elements. In this series, however, tumors were best considered variants of MEC

based on predominance of mucoepidermoid elements with no more than 10% of an acinar component as well as the presence of *MAML2* gene rearrangements in both components without *MSANTD3* or *NR4A3* rearrangements.

Here we present yet another scenario that juxtaposes AciCC and MEC morphology. This time, we show that the base tumor is AciCC with squamoglandular differentiation. Aside from molecular findings, there are some differences

Table 1 Characteristics of utilized antibodies

Antibody	Clone	Dilution	Company
P40	BC28	Pre-dilute	Biocare Medical, Pacheco, CA
SOX-10	BC34	Pre-dilute	Biocare Medical, Pacheco, CA
NR4A3	SC-393,902 [H-7]	1:50	Santa Cruz Biotechnology, Dallas, TX
Synaptophysin	Polyclonal	Pre-dilute	Ventana, Tuscon, AZ
Cytokeratin 7	OV-TL12/30	1:40	Dako, Carpinteria, CA
CAM 5.2	CAM 5.2	1:10	Becton Dickinson, Franklin Lakes, NJ
DOG-1	K9	1:100	Leica, Allendale, NJ
S100	Polyclonal	Pre-dilute	Dako, Carpinteria, CA
Smooth muscle actin	1A4	1:40	Dako, Carpinteria, CA
P16	E6H4	Pre-dilute	Ventana, Tuscon, AZ

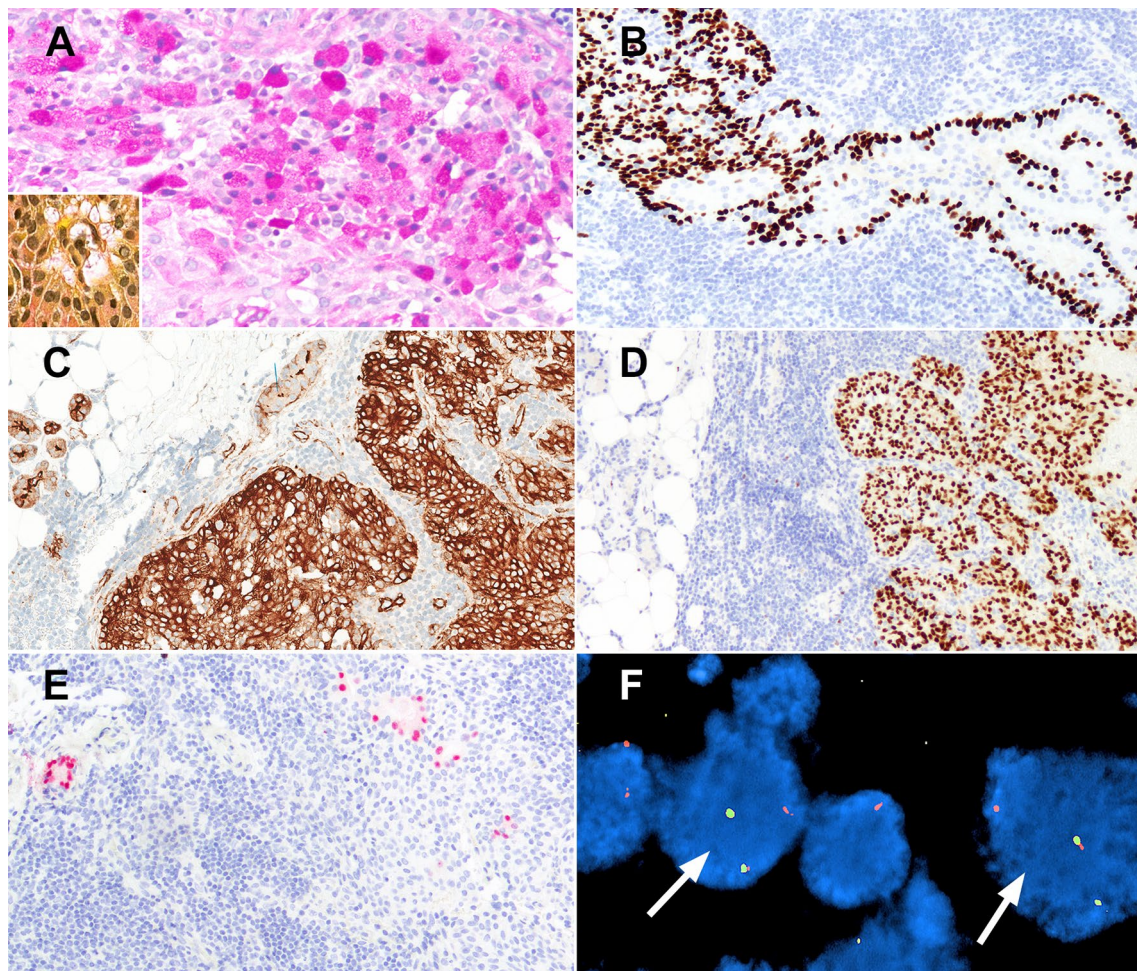


Fig. 2 Ancillary findings in case. **A** PAS after diastase highlights acinar components (10×). Inset (20×) a mucicarmine stain shows faint wispy mucin in the rare mucous cells. **B** P40 highlights the majority of the tumor, sparing ductoacinar elements (10×). **C** DOG-1 (10×) and **D** NR4A3 (10×) are diffusely positive (normal acini on right for

comparison). **E** SOX-10 (10×) however shows only scattered ductal elements with staining (normal intercalated ducts on right for comparison). **F** Breakapart fluorescence in situ hybridization for *NR4A3* is positive for a rearrangement as demonstrated by a split orange green signal (arrows) in the majority of cells

morphologically and immunohistochemically between this squamoglandular variant of AcicC and previously described MAC. 10/11 MAC showed a clear cell/oncocytoid vacuolar

predominant morphology. [12] In contrast, this current case shows more prominent epidermoid type elements and had more of a basaloid appearance. Furthermore, this

squamoglandular variant of AciCC showed a larger proportion of acinar elements, albeit still not the majority component. Finally, while DOG1 in MAC is strongest in the acinar components with focal staining of mucoepidermoid elements, the current showed diffuse strong expression throughout. Surprisingly, it showed only focal SOX-10 staining, while most MAC show fairly extensive SOX-10 reactivity. Reasons for this would be speculative, but may be related to the extent of epidermoid elements seen in this case. Interestingly case 10 in the series of MAC [12] also showed a prominent epidermoid component that was SOX-10 negative; SOX-10 was only positive in the acinar component.

Ultimately distinction between MAC and squamoglandular variant of AciCC may have little impact on management. One concern however that may be raised is that the current case is a form of HGT, but here the squamoglandular areas are simply not high grade. While admittedly limited follow-up precludes confirmation of indolent behavior, the small size and completeness of excision suggests an outcome incongruent with AciCC-HGT.

The differential diagnosis for our case does consist of a few other more ominous considerations. Given the basaloid appearance and squamoid phenotype, a key consideration is a metastatic squamous cell carcinoma or even a skin adnexal carcinoma with basaloid morphology. Aside from the presence of an acinar component, the squamoid elements in this squamoglandular variant of AciCC are fairly bland. P16/high risk human papillomavirus testing may be of value for this distinction, and in this case, p16 was negative. Neuroendocrine carcinomas, primary and metastatic are morphologic considerations that can be excluded immunohistochemically. While acinic cell carcinomas with neuroendocrine elements have been described, the neuroendocrine component is typically minor in such cases. [24] NUT carcinomas are often phenotypically squamous and have somewhat of a basaloid appearance. However, while some NUT carcinomas may be somewhat monomorphic, they still tend to have more mitotic activity and are generally more infiltrative than our case.

Conclusions

In summary, squamoglandular variant of AciCC is a previously undescribed variation on the theme of two distinct morphologies in one tumor. This tumor combines both MEC-like components with standard AciCC elements. However, unlike MAC which can be regarded as a variant of MEC, this tumor is more related morphologically and molecularly to AciCC. Given their blandness, the squamoid and mucous elements here are not indicative of HGT, though this may represent a diagnostic consideration. Similarly given the somewhat basaloid appearance

of this case, squamous metastases, NUT carcinoma, and neuroendocrine tumors are potential pitfalls.

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Declarations

Conflict of interest Authors declare that they have no conflict of interest.

Ethical Approval IRB Exempt (case report).

Consent to Participate Not applicable.

Consent for Publication Not applicable.

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