Warthin tumor-like mucoepidermoid carcinoma

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Abstract: Mucoepidermoid carcinoma (MEC) shows a wide morphologic spectrum, including epithelium with oncocytic or squamous metaplastic changes overlying a prominent cystic architecture, as well as tumor-associated lymphoid tissue. We illustrate a case of mucoepidermoid carcinoma of the parotid in a 17 year-old female, in which all these features occurred extensively, such that they accounted for almost the entire neoplasm, and closely mimicked Warthin tumor histologically. This highlights the need for diagnostic awareness of this particular morphologic variant of MEC, as patients could potentially be inappropriately discharged from follow-up if diagnosed with a benign neoplasm.

Keywords: Mucoepidermoid carcinoma; Warthin tumor; oncocytic variant; metaplastic; histological mimic, pathology; *CRTC1-MAML2*.

We highlight a case of mucoepidermoid carcinoma (MEC) that originally masqueraded as a Warthin tumor by virtue of its unusual morphology of cystic structures lined by bilayered or stratified cuboidal cells, often with an oncocytic appearance, with abundant underlying tumor-associated lymphoid tissue. This arose within a 17 year-old female who presented with a parotid mass. Conservative excision of the mass showed a neoplasm with multiloculated cystic architecture, with low-power appearance remarkably similar to that of Warthin tumor (Fig. 1A). The cysts were lined by stratified or bilayered epithelium and showed extensive underlying supporting stroma packed with small lymphocytes with germinal center formation (Figs. 1B-C). At higher magnification, the cells were cuboidal, with minimally atypical ovoid or rounded vesicular nuclei and abundant eosinophilic cytoplasm, often with an oncocytic morphology. In areas the epithelial lining had a more squamoid appearance, morphologically similar to squamous metaplasia in Warthin tumor. Mitotic figures and necrosis were absent. In addition, one small 1 mm focus had a different morphology, comprising smaller cystic or

glandular structures filled with mucin and lined by attenuated epithelial cells and occasional apparent mucocytes, with adjacent epidermoid cells and intermediate cells, and with a paucity of lymphoid tissue (Figs. 1D-E); this was the principal morphologic feature to raise the suspicion of MEC, and was the only such focus on examination of multiple representative sections of tumor. The patient presented with recurrent tumor four years later. The excised recurrent tumor showed very different architectural features from the original neoplasm, with prominent areas with classical mucoepidermoid morphology, including sheet-like areas of intermediate and epidermoid cells and mucocytes (Fig. 1F).

This case highlights that mucoepidermoid carcinoma can closely resemble Warthin tumor, and that Warthin-like architectural and cytological features can account for almost the entire neoplasm. This is particularly challenging diagnostically because Warthin tumor and MEC are not normally considered differential diagnoses of one another. Warthin tumor typically occurs in an older population and is uncommon in the first three decades of life, whereas MEC occurs across a wider age range and is the most common salivary gland neoplasm in pediatric patients. MECs can have abundant tumor-associated lymphoid tissue, raising the differential diagnosis of Warthin tumor or lymphoepithelial neoplasms. The Warthin tumor-like appearances of this variant of MEC can be further enhanced by the bland oncocytic features with paucity of mitotic figures, and absence of tumor necrosis and perineurial invasion. Although Warthin tumors can undergo metaplastic changes with abundant squamous and even mucinous metaplasia, these features tend to be more focal, with areas of residual classic oncocytic epithelium, and these metaplastic changes are also often associated with trauma such as hemorrhage, necrosis and fibrosis. Careful microscopic inspection of multiple sections of tumor can reveal small numbers of mucous cells; the presence of these in an oncocytic neoplasm (which can account for <1% of the tumor) may represent an important diagnostic clue to oncocytic MEC,[1] and mucin stains such as

mucicarmine can aid diagnosis.[1] Awareness of Warthin tumor-like variant MEC is therefore crucial, coupled with the knowledge that the occurrence of Warthin tumor would be rare in young patients. The overlap between MEC and Warthin tumor with metaplastic change has been recognized for some time, but more recent knowledge of the genetics of MECs has allowed more accurate diagnosis. Evidence of *MAML2* gene rearrangement with fluorescence *in situ* hybridization can be used to distinguish oncocytic MEC from other oncocytic lesions including Warthin tumor.[2] Ishibashi *et al*. recently noted that 'metaplastic Warthin-like' tumors harboring *CRTC1-MAML2* had features more in keeping with MEC than Warthin tumor.[3] Five of 15 'metaplastic Warthin-like' tumors in their series harbored *CRTC1-MAML2* gene fusions, with age and gender distributions of fusion-positive cases similar to those of fusion-positive MEC, and differing both from fusion-negative metaplastic Warthin-like tumors and from cases of typical Warthin tumor. Additionally, foci of low-grade MECs were found only in fusion-positive metaplastic Warthin-like neoplasms. These investigators also showed that all fusion-negative cases retained, at least focally, some of the oncocytic bilayered epithelium typical of Warthin tumor, but this was absent in fusion-positive cases and therefore it was possible with a high success rate to distinguish the diagnoses morphologically. They propose that such cases are better regarded as MECs rather than metaplastic Warthin tumors, and the case presented here would be in keeping with such an example.

Figure legends:

Fig. 1: Warthin tumor-like mucoepidermoid carcinoma. **Fig. 1A:** At low magnification, the neoplasm shows extensive Warthin tumor-like architecture, with cystic formations with walls containing dense lymphoid tissue composed of small lymphocytes, with prominent germinal centers, and lined by stratified or bilayered epithelium. **Figs. 1B-C:** The lining epithelium is

either stratified or shows two layers, and is composed of cuboidal cells with bland, ovoid vesicular nuclei and abundant eosinophilic cytoplasm, often with an oncocytic appearance. **Figs. 1D-E:** Only on inspection of multiple sections is one small focus seen to show a different architecture, with a collection of smaller cysts in fibrous stroma. These cysts are lined by partially attenuated epithelium and harbor occasional mucocyte-like cells (Fig. 1D, arrowed) or are adjacent to clusters of squamoid cells (Fig. 1E, arrowed). **Figs. 1F:** The recurrent tumor which occurred four years later shows strikingly different architectural features from the original neoplasm, with much more easily discernible 'classical' features of mucoepidermoid carcinoma. The Warthin tumor-like architecture was essentially absent, and now there are prominent solid areas with sheets of intermediate and epidermoid cells and mucocytes.

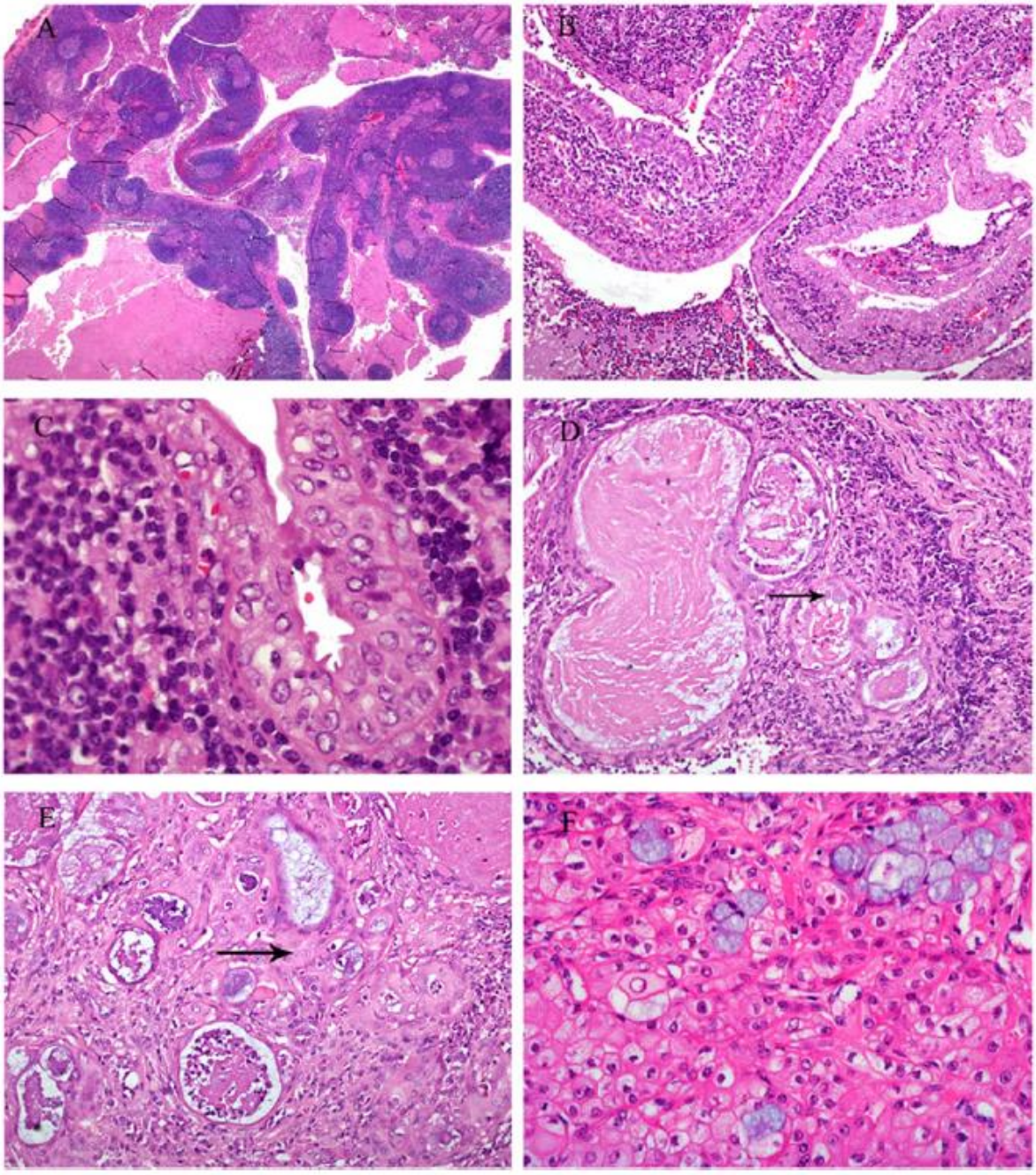

Fig. 1: Warthin tumor-like mucoepidermoid carcinoma.

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