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Warthin-like Variant of Mucoepidermoid Carcinoma of the Parotid Gland

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A 57-year-old woman with a 2-year history of a left infra-auricular mass with no associated symptoms presented with a 6.0 cm ´ 4.0 cm ´ 3.0 cm firm, non-tender, movable mass. No imaging was done. Fine needle aspiration biopsy (FNAB) revealed sheets of epithelial cells that had abundant dense grayish-blue cytoplasm in a mucinous background with abundant lymphocytes *(Figure 1),* suggestive of salivary gland neoplasm with oncocytic or oncocytoid features (Category IVB, Salivary Gland Neoplasm of Uncertain Malignant Potential).[1]

Total parotidectomy revealed a 4.3 X 3.2 X 3.0 cm deep lobe lesion with a tan-grey to dark brown, smooth and dull external surface. Cut sections showed a cream-white to pink, lobulated, heterogenous cut surfaces. Microscopically, the lesion was unencapsulated with poorly demarcated borders. The neoplastic cells were arranged in haphazard sheets and surrounded by abundant lymphocytes. The tumor cells had abundant eosinophilic and granular cytoplasm compatible with oncocytes with mild to moderate nuclear atypia. There were occasional cystic spaces that contained mucin though mucocytes were not readily apparent. *(Figure 2)* Necrosis, perineural and lymphovascular space invasion or anaplasia were not evident.

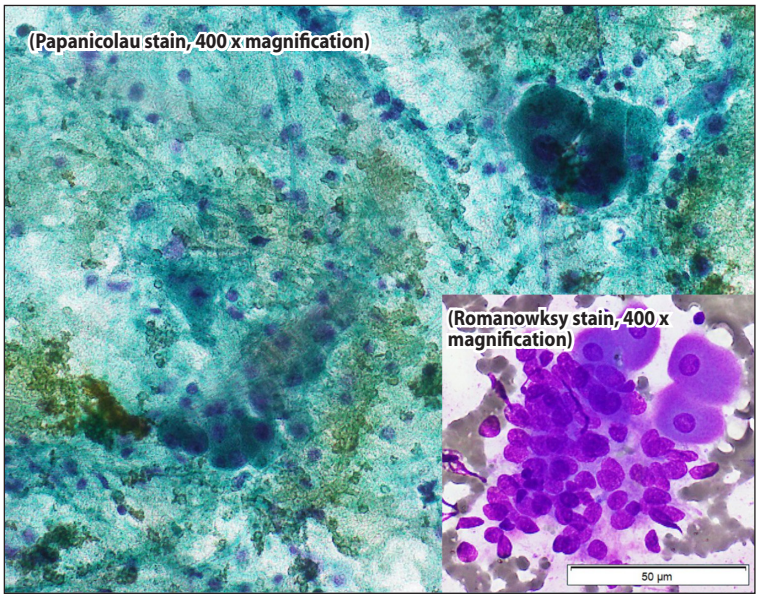

Figure 1. The epithelial cell clusters have a mucinous background with abundant lymphocytes (Papanicolau stain, 400 x magnification). Inset shows round cells with round nuclei and abundant dense greyish-blue cytoplasm with well-defined cytoplasmic borders (Romanowksy stain, 400 x magnification).

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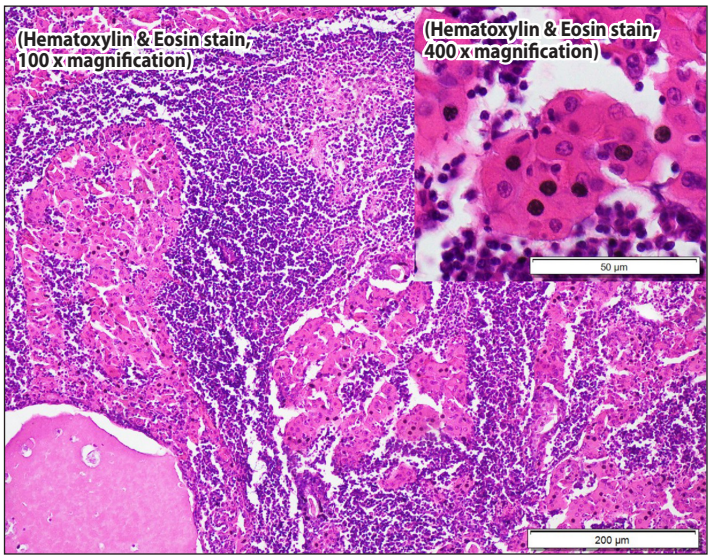

Figure 2. The neoplastic cells are arranged in haphazard sheets surrounded by abundant lymphocytes (Hematoxylin & Eosin stain, 100 x magnification). Inset shows oncocytic cells with abundant eosinophilic granular cytoplasm and nuclear atypia (Hematoxylin & Eosin stain, 400 x magnification).

Immunohistochemistry studies showed frequent tumor cells with moderate-to-strong cytoplasmic staining for Cytokeratin 5/6 and moderate-to-strong nuclear staining for p63, highlighting squamous epithelial cells, while scattered admixed cells showed patchy, strong, cytoplasmic staining for MUC4 and focal, strong, cytoplasmic staining for MUC5AC, highlighting mucous cells. *(Figure 3)* Periodic Acid-Schiff (PAS)-positive, diastase-resistant staining highlighted the extracellular mucin and intracytoplasmic mucin in mucous cells, while DOG1 and SOX10 were negative. *(Figure 4)* Molecular testing by fluorescence in situ hybridization (FISH) with dual-color break-apart probes (Commercial ZytoLight SPEC *MAML2* Dual Color Break Apart Probe, Zytovision) showed an abnormal break-apart signal of one red and one green fluorochrome at a distance from each other indicating the Mastermind Like Transcriptional Coactivator 2 or *MAML2* gene rearrangement. *(Figure 5)* Based on the immunohistomorphological and molecular features, a diagnosis of Warthin-like variant of Mucoepidermoid Carcinoma (WL-MEC), low-grade was rendered.

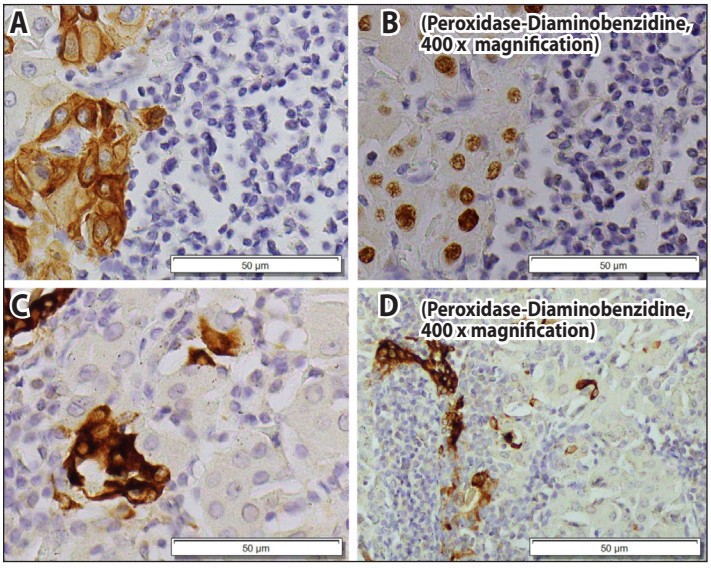

Figure 3. A. Cytokeratin 5/6 shows frequent, moderate to strong cytoplasmic staining; **B** p63 shows diffuse, moderate to strong nuclear staining in the intermediate and squamoid cells (Peroxidase-Diaminobenzidine, 400 x magnification); **C.** MUC4 shows patchy, strong, cytoplasmic staining; and **D.** MUC5AC shows focal, strong, cytoplasmic staining in mucous cells (Peroxidase-Diaminobenzidine, 400 x magnification).

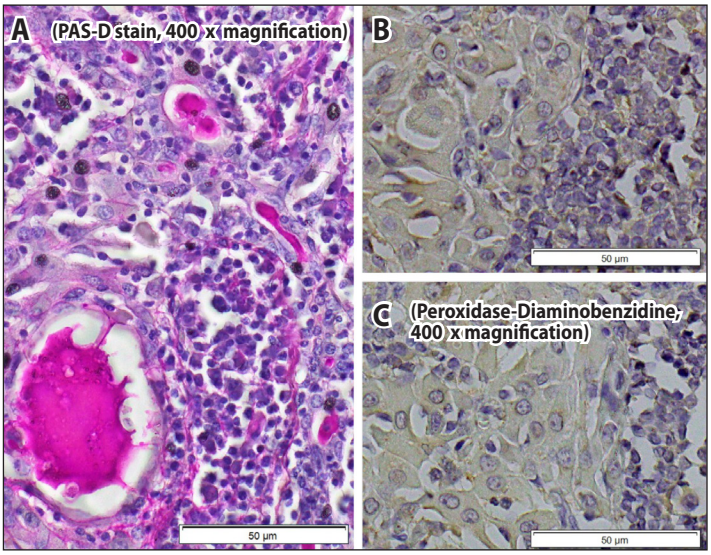

Figure 4. A. PAS-positive, diastase-resistant staining highlights intracytoplasmic mucin in mucous cells and extracellular mucin in ductal structures (PAS-D stain, 400 x magnification); **B.** DOG1; and **C.** SOX10 are both negative (Peroxidase-Diaminobenzidine, 400 x magnification).

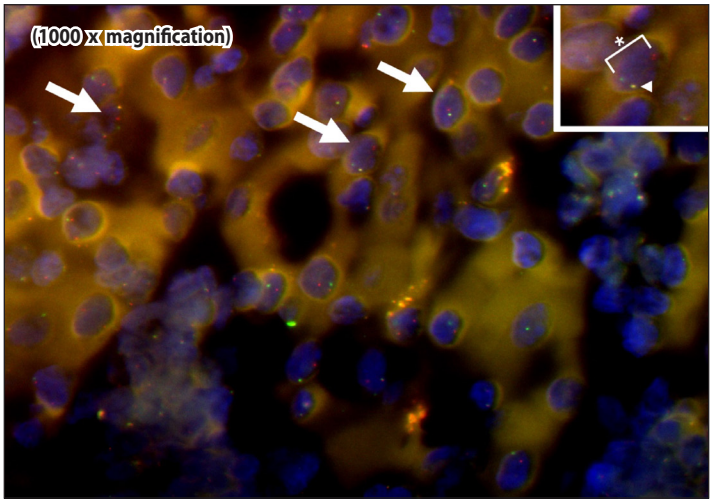

Figure 5. FISH images show tumor cell nuclei (white arrows) with one red and one green break-apart signal at a distance from each other. Inset shows one red and one green break-apart signal (white asterisk with square bracket), and one yellow fused signal (white arrowhead) that confirm *MAML2* gene rearrangement (1000 x magnification).

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Warthin-like variant of Mucoepidermoid Carcinoma was recently categorized as a novel and low-grade form of mucoepidermoid carcinoma and proposed by Ishibashi *et al.* in 2015.[2] The tumor was described as having glandular or cystic or papillary cystic arrangement of oncocytic epithelium and a dense lymphoid infiltrate.[2] Only 28 cases are reported in the literature and most appear to have a slow biological behavior with no recurrence or metastasis after total parotidectomy.[3] Although the literature supports classifying WL-MEC as a low-grade form of MEC, in the current case, the authors decided to still mention the grade in the diagnosis to facilitate communication with the managing clinical service as the management of WL-MEC follows that of conventional MEC wherein low-grade lesions are treated with surgery alone.[3]

Because of the presence of oncocytes in a dense lymphoid background, the most cogent morphological differential diagnosis is a Warthin Tumor – a benign salivary gland tumor characterized by glandular spaces lined by oncocytes and similarly surrounded by abundant lymphocytes. The most helpful finding in distinguishing the two is that WL-MEC lacks the well-arranged, bilayered oncocytic epithelium characteristic of Warthin Tumor (WT) and is instead characterized by a haphazard proliferation of the tumor cells.[3] In addition, the infiltrative border of a carcinoma differs from the well-circumscribed and encapsulated one of a benign lesion such as WT.

A potential pitfall is when a WT is infarcted and undergoes squamous and mucinous metaplasia. This change usually occurs after FNAB and thus tends to be more focal accompanied by hemorrhage, necrosis and infarction, and has identifiable areas of residual classic bilayered oncocytic epithelium. In problematic cases, *MAML2* gene rearrangement studies can be done which is not seen in classic WT.[4,5] In the current case, the authors opined that molecular testing can also be done for educational and research purpose, and to help build institutional experience.

Another differential diagnosis is the oncocytic pattern of Acinic Cell Carcinoma (ACC) in which the neoplastic cells are predominantly oncocytic with few cells having the classic basophilic and granular, serous-type, cytoplasm. ACC can also have a prominent lymphoid proliferation. In contrast to MEC, ACC stains positive for DOG1 and SOX10 and negative for Cytokeratin 5/6 and p63.[6]

High-molecular weight keratins such as Cytokeratin 5/6 and p63 highlight the cytoplasm and nucleus of the oncocytic epithelium, respectively, which supports their squamous lineage while the admixed mucous cells lining the cystic spaces are highlighted by MUC4, MUC5AC and PAS staining with diastase resistance.[7]

The chromosomal translocation t(11;19) (q21;p13) results in a *CRTC1-MAML2* gene fusion which is specific for MEC including the Warthin-like variant and correlates with low- to intermediate-grade histology and improved prognosis.[5] Although the break-apart FISH done on our case demonstrated *MAML2* gene rearrangement, one limitation is our test system's inability to specifically identify the partner gene involved.

The patient subsequently underwent 33 cycles of adjuvant radiation therapy. On follow-up, no recurrence or lymph node metastasis have yet been reported that, though preliminary, may be consistent with the lesion's low-grade biology.

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