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Surgical and Experimental Pathology (2022) 5:17
https://doi.org/10.1186/s42047-022-00119-5

Surgical and Experimental Pathology

CASE REPORT

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MAML2 negative oncocytic mucoepidermoid carcinoma of submandibular gland

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Abstract

Background: Oncocytic mucoepidermoid carcinoma is a rare variant of mucoepidermoid carcinoma. Only a few cases are reported involving mostly the parotid gland with only four cases reported in the submandibular gland. *Mastermind-like 2 (MAML2)* translocation is detected in about 66% mucoepidermoid carcinoma and many oncocytic mucoepidermoid carcinoma.

Case presentation: We present a rare case of *MAML2* negative oncocytic mucoepidermoid carcinoma of the submandibular gland in a 73-year-old female. CT revealed a large left submandibular gland mass. Submandibular gland resection with marginal mandibulectomy and ipsilateral neck dissection was performed. Grossly, a solid-cystic submandibular gland tumor was identified. Microscopic examination revealed an infiltrative proliferation of oncocytes. Foci of squamoid and intermediate cells with rare mucocytes were present. Two ipsilateral cervical lymph nodes and mandible were involved. Immunohistochemistry and special stains demonstrated positivity for p63, p40, CK5/6, mucicarmine and alcian blue. No *MAML2* gene rearrangement was identified.

Conclusion: An awareness that *MAML2* negative mucoepidermoid carcinoma exists will prevent misdiagnosis and incorrect treatment as many of its differential diagnoses are benign.

Keywords: Oncocytic mucoepidermoid carcinoma, Submandibular gland, *MAML2*

Background

Mucoepidermoid carcinoma (MEC) is the most common malignant salivary gland tumor (D'Antonio et al., 2015). MEC consists of squamoid cells, intermediate cells, and mucous cells in varying proportions (Liao et al., 2016). MEC may occasionally show presence of other cell types including clear cells and oncocytes. The diagnosis becomes challenging when these cells predominate (Luna, 2006; Coca-Pelaz et al., 2015; Gill et al., 2017). Oncocytic mucoepidermoid carcinoma (OMEC) has a predominance of oncocytes with no well-defined percentage (Weinreb et al., 2009). OMEC is a rare variant. Only a few cases have been reported involving mostly the parotid gland. Submandibular gland is a rare site for OMEC with only four cases reported in the English literature (Corcione et al., 2007; Krishnanand et al., 2007; Jing et al., 2012; Avila et al., 2019). Table 1 summarizes them. *Mastermind-like 2 (MAML2)* translocation is detected in about 66% MEC and many oncocytic MEC (Seethala et al., 2010; García et al., 2011). Skalova et al. found only *MAML2* rearranged OMEC with no *MAML2* negative OMEC in their study (Skálová et al., 2020). However, Garcia et al. found 4 out of 14 OMEC that were *MAML2* negative. All 14 of their cases were parotid tumors (García et al., 2011). We report a

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Table 1 Cases of submandibular OMEC reported in English literature

Authors	Age/Sex	Clinical presentation	Treatment	Follow-up	MAML2 rearrangement
Corcione et al., 2007	74 years/Male	Painless, slow growing submandibular mass for 2 years	Excision	–	Not done
Avila et al., 2019	40 years/Male	painful submandibular mass for 6 months	Surgical resection	No recurrence	Not done
Jing H., 2012	70 years/Male	Painless submandibular mass	excision	free of disease at the 19-month follow-up	Not done
Krishnanand et al., 2007	53 years/Female	Painless submandibular mass for 3 years	excision	No recurrence on 2 years follow up	Not done
Present study	73 years/Female	Submandibular mass for 11 months	Left submandibular gland resection with marginal mandibulectomy and ipsilateral neck dissection was performed	Patient expired from unrelated clinical and surgical complications	No rearrangement by FISH

rare case of *MAML2* negative oncocytic MEC of the submandibular gland. To the best of our knowledge *MAML2* negative OMEC has not been reported in the submandibular gland.

Case presentation

We present a rare case of *MAML2* negative OMEC of the submandibular gland in a 73-year-old female with an 11-month history of a left neck mass. CT revealed a large centrally necrotic left submandibular gland mass with a thick enhancing soft tissue rim. Fine-needle aspiration cytology confirmed malignancy. Left submandibular gland resection with marginal mandibulectomy and ipsilateral neck dissection was performed.

Grossly, a circumscribed, solid-cystic tumor measuring $13.5 \times 11 \times 4.5$ cm, arising from the submandibular gland was identified. Microscopic examination revealed an un-encapsulated and infiltrative proliferation of oncocytes forming cords, nests, and sheets. The oncocytes were polygonal in shape and revealed abundant eosinophilic and granular cytoplasm with centrally located nuclei having prominent nucleoli (Fig. 1A, B & C). Tubulocystic areas with rare vacuolated cells and foci of squamoid and intermediate cells were present (Fig. 1D, E & F). A diagnosis of mucoepidermoid carcinoma, intermediate grade, with features of pure oncocytic variant was made. No perineural invasion was identified. Two ipsilateral cervical lymph nodes and mandible were involved. Mucicarmine and alcian blue special stains demonstrate rare intraluminal and intracytoplasmic mucin (Fig. 2A & B). Immunohistochemical (IHC) stains demonstrated immunoreactivity for p63 (diffuse; Fig. 3A), p40 (Fig. 3B), CK5/6 (diffuse, Fig. 3C), and weak and rare immunoreactivity for GATA 3 and GCDFP-15. No immunoreactivity was seen for CK7, calponin, S-100, TTF-1, and thyroglobulin, supporting our diagnosis and ruling out salivary duct carcinoma, mammary analog secretory carcinoma, plasmacytoid myoepithelioma, and metastatic thyroid neoplasm. Table 2 shows specifications of IHC antibodies used. No rearrangement of the *MAML2* gene on fluorescent in-situ hybridization testing was identified, when tested at two independent centers. Rearrangements of the *MAML2* gene on 11q21 were evaluated using *MAML2* break-apart FISH probes (Empire Genomics, Buffalo, NY) on formalin-fixed and paraffin-embedded (FFPE) tissue slides.

The patient also had co-morbidities including HCV infection, cirrhosis, coronary artery disease with stent placement and hypertension. She presented 10 days after discharge with left femoral neck fracture and underwent left hip hemiarthroplasty. The pathologic examination revealed signs of fracture without any pathology in the bone. A month later she had right femoral neck fracture which was surgically repaired. Patient tolerated the procedure well and was admitted to the floor. Five days later patient clinically declined and found to be in septic shock secondary to *C. difficile* colitis. Total abdominal colectomy was performed. However, patient continued to clinically decline and expired the next day.

Discussion and conclusion

MEC is composed of squamoid, intermediate and mucous cells in varying proportions. Other cell types that could be found are clear cells, columnar cells,

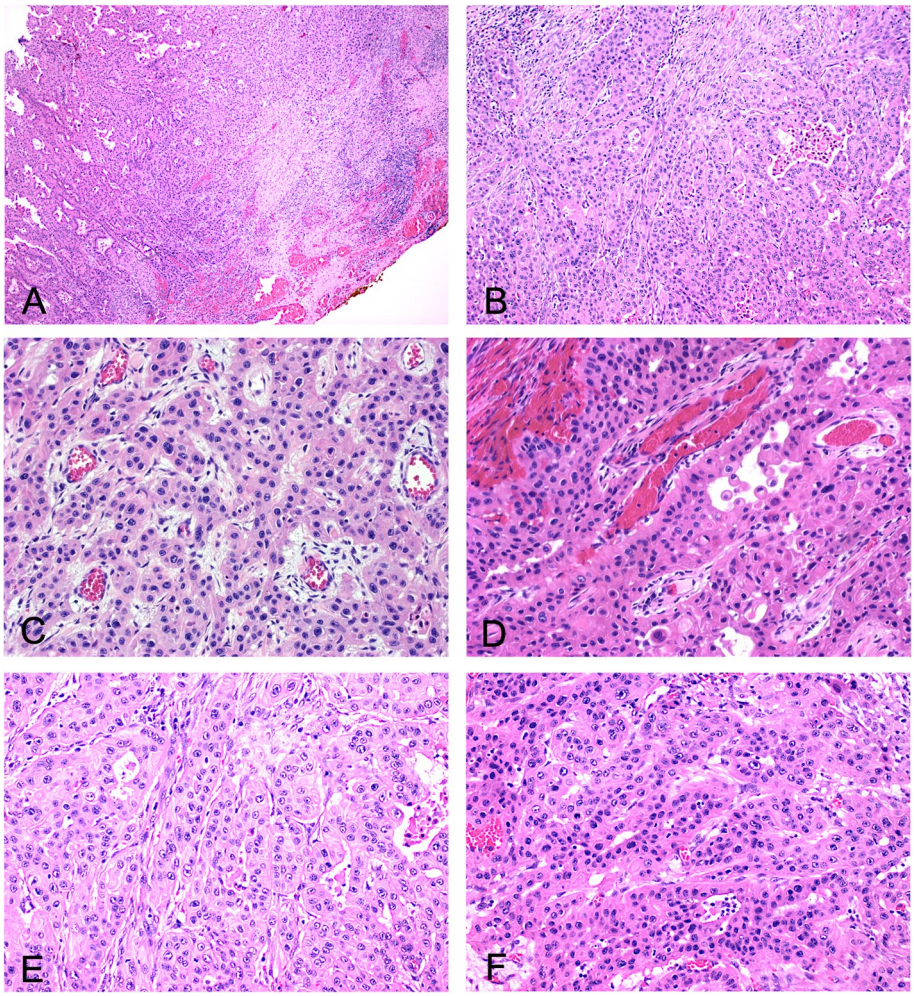

Fig. 1 Morphology on hematoxylin & eosin staining. **A, B** & **C** A solid-cystic infiltrative proliferation of oncocytes forming nests, cords, and trabeculae (H&E; 40X, 100X & 200X). **D** Tubulocystic area showing cysts lined by oncocytes and rare vacuolated cells (H&E; 200X). **E** Focus of squamoid cells (H&E; 200X). **F** Focus of intermediate cells (H&E; 200X)

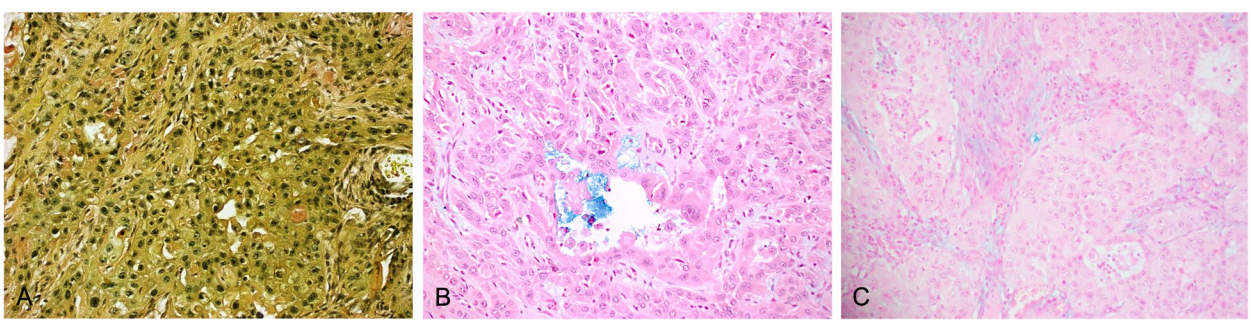

Fig. 2 Special stains**. A** Mucicarmine highlighting intracellular mucin (400X). **B** & **C** Alcian blue highlighting intraluminal and intracellular mucin (400X & 200X)

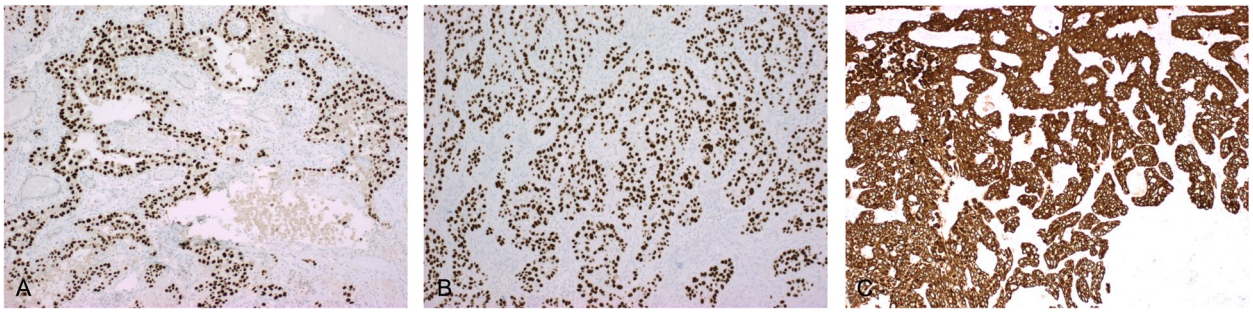

Fig. 3 Immunohistochemical stains. **A** Diffuse nuclear p63 immunostain highlighting squamoid (IHC; 100X). **B** Diffuse nuclear immunostain highlighting squamoid cells (IHC; 100X). **C** Diffuse cytoplasmic and membranous CK5/6 immunostain highlighting squamoid cells (IHC; 100X)

Table 2 IHC antibody specifications

IHC antibody	Manufacturer	Concentration (µg/mL)/ Dilution
p63	Biocare	Ready to use
p40	Ventana	0.4
CK5/6	Ventana	10.4
CK7	Dako	1:100
GATA3	Cell Marque	3.4
GCDFP	Biocare	1:40
Calponin	Cell Marque	0.19
S-100	Ventana	10.0
TTF1	Ventana	7.0
Thyroglobulin	Cell Marque	0.23

goblet cells, and oncocytes (Qayoom et al., 2021). Occasionally, clear cells and oncocytes predominate with rare mucinous cells which are the only clue to the diagnosis of MEC. Such cases pose a diagnostic challenge for pathologists. OMEC presents in the age range of 20 to 80 years with a male predilection (Kwon et al., 2010). Most are cystic and have a favourable prognosis (Weinreb et al., 2009). OMEC can be mimicked by many benign and malignant neoplasms, including oncocytoma, oncocytic variant of cystadenoma, oncocytic carcinoma, myoepithelioma, oncocytic pleomorphic adenoma, metaplastic Warthin's tumor, salivary duct carcinoma, and metastatic renal cell carcinoma. Distinguishing these from OMEC is imperative due to prognostic differences. P63 is considered a potential marker that could differentiate between these entities. The epidermoid/squamoid cells of OMEC are immunoreactive for p63. Oncocytomas and oncocytic carcinoma are also p63, however, the staining pattern is predominantly peripheral/basal (McHugh et al., 2007). Metastatic renal cell carcinoma is p63 negative (McHugh et al., 2007). Myoepithelioma and squamous cell carcinoma stain diffusely with p63 but both lack mucin-producing cells. Myoepithelioma also stains for other myoepithelial markers, such as calponin and actin. Warthin's tumors typically don't have mucous cells or intercellular bridges in the oncocytic cells and are non-infiltrative (Weinreb et al., 2009). Pleomorphic adenomas have chondro-myxoid stroma and are generally non-infiltrative (Skálová et al., 1999). The Table 3 summarises the differential diagnosis of OMEC.

Rearrangement in *MAML2* gene, a component of the Notch signaling pathway, has been promising in diagnosing MEC and its variants accurately. *MAML2* translocation by FISH is detected in approximately 66% typical MEC cases and about 71% of oncocytic MEC (Liao et al., 2016; García et al., 2011). In contrast, most of the imitators of MEC are negative for *MAML2* translocation. Thus, Liao et al. suggested that *MAML2* translocation can be used as a diagnostic tool to detect OMEC. However, our case of *MAML2* negative OMEC introduces an important consideration that *MAML2* negative OMEC do exist, and the diagnosis should not be solely based on the presence of *MAML2* translocation.

Previous studies considered *MAML2* to confer a favourable prognosis (Seethala et al., 2010). However, recently the prognostic significance of *MAML2* rearrangement has been challenged (Skálová et al., 2020). Our case, which was *MAML2* negative, had an aggressive course with spread to mandible bone and regional lymph nodes.

In summary, we present a rare case of *MAML2* negative OMEC of the submandibular gland composed primarily of oncocytes with only rare mucous cells, epidermoid cells and intermediate cells. Further studies

Table 3 Differential diagnoses of OMEC

	Cysts	Squamoid cells and mucous cells	Microscopic appearance	Immunohistochemical stain
Oncocytic mucoepidermoid carcinoma	+	+	Solid cystic tumor predominantly showing proliferation of oncocytes with cystic spaces lined by mucous cells, squamoid cells, and intermediate cells	Diffuse p63, p40, CK5/6, mucin stain positive in mucous cells; frequently positive for MAML2 rearrangement
Oncocytoma	occasional	–	Encapsulated neoplasm growing in an organoid pattern separated by thin fibrous septae. Squamoid and mucous cells are absent.	Peripheral/basal p63, p40, CK5/6 staining; negative for mucin stain
Oncocytic carcinoma		–	Single, or multinodular unencapsulated, neoplasm. Trabeculae, sheets, and nests of pleomorphic oncocytes infiltrating the salivary gland parenchyma. Squamoid and mucous cells are absent.	Positive for p63, p40 and CK5/6 in peripheral/basal distribution; negative for mucin stain
Metaplastic Warthin's tumor	+	+	Papillary cystic neoplasm demonstrating a bilayered epithelium lined by oncocytic and basal cells in a lymphoid stroma. Squamous and mucin producing cells may be identified.	Metaplastic squamous epithelium is positive for p40, p63 and CK5/6 staining. Mucicarmine is positive in mucous cells.
Secretory carcinoma	+/−	–	Lobulated growth of neoplastic cells showing eosinophilic to vacuolated cytoplasm with vesicular bland nuclei. It exhibits cystic, solid, tubular, follicular and papillary architectural patterns Pale eosinophilic periodic acid-Schiff (PAS) positive and diastase resistant intraluminal secretions are present.	Positive for GATA 3, mammoglobin, and S100 immunostains; ETV6 translocation (usually with partner gene NTRK3); myoepithelial cell stains (p63, S100, actin) are negative
Oncocytic pleomorphic adenoma	–	+	Encapsulated triphasic neoplasm with epithelial, myoepithelial and chondromyxoid stromal component. Squamous and mucinous metaplasia may be seen.	Peripheral/basal p63, p40 staining; S100 is positive in myoepithelial cells, c-kit positive in ductal component
Plasmacytoid myoepithelioma	–	–	Large plasmacytoid cells in cords, clusters and sheets in a myxoid stroma.	Positive p63, actin, calponin and S100 staining
Salivary duct carcinoma	+	–	Invasive oncocytic tumor cells arranged in cords, cribriform glands and nests showing high grade nuclear features in a desmoplastic stroma.	Positive for CK7, GCDFP and androgen receptor; p63, p40 and CK5/6 are mostly negative

are required to understand the pathogenesis of MEC and the prognostic significance of *MAML2* rearrangement in its pathogenesis. An awareness that *MAML2* negative OMEC exists will prevent misdiagnosis and incorrect treatment as many of the differential diagnoses of OMEC are benign.

Abbreviations
MEC: Mucoepidermoid carcinoma; OMEC: Oncocytic Mucoepidermoid carcinoma; MAML2: Mastermind-like 2.

Acknowledgements
None.

Authors' contributions
All authors contributed equally in preparing the manuscript. The author(s) read and approved the final manuscript.

Funding
None.

Availability of data and materials
Not applicable.

Declarations

Ethics approval and consent to participate
Not applicable.

Submission declaration and verification
Parts of this article were previously presented as an abstract/poster at CAP 2021 virtual abstract program.

Consent for publication
Not applicable (no identifying information is present in the case report).

Competing interests
None.

Received: 31 January 2022 Accepted: 5 July 2022
Published online: 20 August 2022

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