CASE REPORT

Oncocytic Mucoepidermoid Carcinoma and Its Diagnostic Challenges

Dharshinie Devan[1,2], Noor Hasni Shamsudin[2], Lai Shau Kong[1], Maizaton Atmadini Abdullah[1]

[1] Histopathology Unit, Department of Pathology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia
[2] Histopathology Unit, Department of Pathology, Hospital Tuanku Ja'afar Seremban, Jalan Rasah, Bukit Rasah, 70300 Seremban, Negeri Sembilan, Malaysia.

ABSTRACT

Mucoepidermoid carcinoma (MEC) is the most common salivary gland malignancy. Often seen in the parotid gland, MECs are characterized by the combination of three cell types namely; mucous, intermediate, and epidermoid cells in varying proportions. Among salivary gland tumours, MEC exhibits a specific translocation resulting in CRTC1::MAML2 fusion gene. Rare variants of MEC are seen with columnar, clear cells and oncocytic cells, which complicates diagnosis, as these entities overlap with other benign and malignant lesions. A 61 years old female presented with right preauricular swelling. Cytologic aspiration was unsatisfactory with cystic contents. On histologic examinations, the tumour composed of >90% oncocytic cells intermixed with mucous cells and squamoid cell population. The tumour cells expressed positivity for CK 5/6, p63, p40, mucicarmine, PAS-D and were negative for S100. Extensive differential diagnosis for oncocytic lesions requires thorough sampling, histological examination, and use of ancillary studies to accurately diagnose salivary gland neoplasms.
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Corresponding Author:
Maizaton Atmadini Abdullah, PhD
Email: maizaton@upm.edu.my
Tel: +603-97692391

INTRODUCTION

Mucoepidermoid carcinoma (MEC) is the most common malignancy of the salivary glands, typically arising in the parotid gland, with a slight female predominance. According to GLOBOCAN datasheet reported in 2022, salivary gland carcinomas are the 28th most common in Malaysia, with 236 new cases reported in 2022, approximately 0.46% of carcinomas. Mucoepidermoid carcinomas are characterized by the presence of three distinct cell types namely mucous, intermediate, and epidermoid cells, all appearing in varying proportions within the tumour [1,2,3,4,5]. Mucoepidermoid carcinomas are graded into low, intermediate and high grade. Cystic spaces filled with abundant mucous cells are typically seen in low grade lesions, whereas the intermediate group consists of more solid areas. In high-grade lesions, the tumour is generally solid composed of intermediate and epidermoid cells with scanty mucous cells. Areas of necrosis and neural involvement are often seen in higher grades [1,2,3,5]. Most of the low and intermediate grade MEC harbour a specific translocation at t(11;19)(q21;p13), expressing the CRTC1::MAML2 fusion gene [5]. Rare variants of MEC have also been encountered when minority or focal proportions of other cells types are seen within the tumour. Examples of such rare variants includes: oncocytic, sebaceous, clear, spindle, melanocytic, goblet, sclerosing, psammomatous, and unicystic [1,2,3,4]. The diagnosis of MEC becomes challenging when any of these components predominate [1,4]. We report a rare case of oncocytic variant of mucoepidermoid carcinoma (OMEC).

CASE REPORT

A 61-year-old Indian female with a chronic history of right preauricular swelling presented with a sudden onset of painful enlargement. Clinically, a salivary gland

neoplasm was suspected, likely pleomorphic adenoma. Fine needle aspiration (FNA) cytology was unsatisfactory, revealing only cystic content. A surgically excised solid cystic mass measuring 40mm x30mm x25mm was received for histopathological examinations, which revealed a solid lobulated malignant tumour measuring 32 mm in largest diameter. Microscopically, the tumour is composed of malignant cells arranged mostly in solid sheets with areas of cystic glandular spaces (Figure 1). The tumour cells were predominantly oncocytic (>90%) displaying polygonal to columnar like cells. In view of the predominant oncocyte population, a panel of immunohistochemical stains were performed to exclude possible differential diagnosis and to arrive at the accurate diagnosis. Population of scattered mucocytes displaying intracytoplasmic mucin were highlighted by a mucicarmine positivity and diastase-resistant PAS staining. The predominantly oncocytic areas of squamoid cells population were highlighted by CK 5/6, whereas the intermediate cells were immunopositive for p63 and p40. (Figure 2). These tumour cells were immunonegative for S-100 and PAX8. Ki 67 proliferation index was noted to be 2% at the highest areas, approximately 0-1 in 10 high power field (hpf) (Figure 2). The tumour showed no significant increase in mitosis or tumour necrosis. Focal perineural invasion was observed however, no lymphovascular invasion, extravasation of mucin pools and extra parenchymal invasion noted. The three lymph nodes submitted were negative for malignancy. This tumour was graded as low grade according to Armed Forces Institute of Pathology (AFIP) and Memorial Sloan Kettering Cancer Center (MSKCC) grading system.

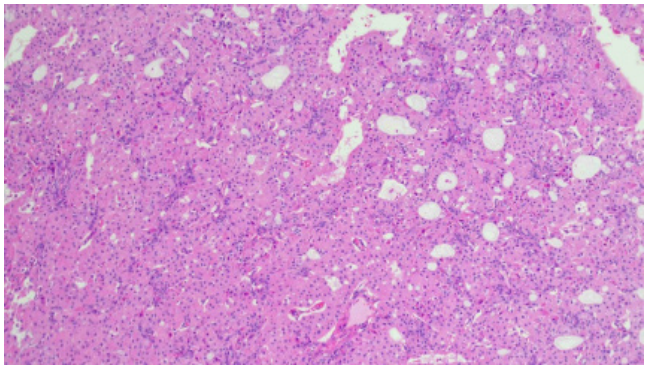

Figure 1 shows a solid tumour with cystic spaces predominantly composed of oncocytic cells displaying bland nucleus with ample eosinophilic cytoplasm and intracytoplasmic mucin. (H&E 100x)

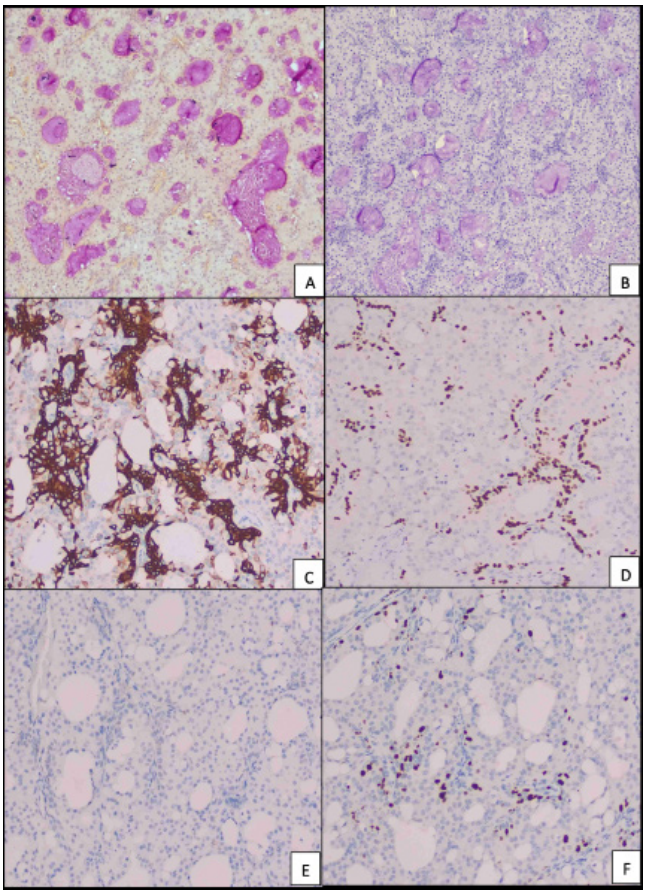

Figure 2A and B shows the intraluminal mucinous secretions highlighted by Mucicarmine stain with PAS-D resistance, respectively. Figure 2C shows the squamoid cells population expressing CK 5/6 stain meanwhile Figure 2D shows the intermediate cell population demonstrated by the p63 immunopositivity. (100x). Figure 2E demonstrate the immunonegativity of this tumour for S100. Figure 2F shows the Ki67 proliferative index of this tumour; approximately 2%. (100x)

DISCUSSION

Oncocytic mucoepidermoid carcinoma is a very rare malignancy often seen in the parotid gland [1,3,4]. This tumour is commonly seen with a slight female predilection across a wide age group affecting children to older adults [5]. The diagnosis is defined by the presence of >50 % oncocytic cells within MEC [1,2]. Oncocytic changes in salivary glands are believed to arise from degenerative cellular alterations, metaplastic transformation, or an adaptive response to an unknown somatic mutation [1]. Oncocytic metaplasia is commonly seen in MEC, occurring due to mitochondrial alterations, resulting in enlarged cells with abundant eosinophilic granular cytoplasm [2]. The presence of this variant does not impact the generally favourable prognosis of MEC [1,2,3].

Low-grade MECs containing oncocytes are often distinguishable from other oncocytoid tumors, provided typical MEC areas are appreciated within the tumor. However, when oncocytic cells predominate with scanty epidermoid, intermediate and mucus cells the diagnosis becomes more challenging, with the need to consider other oncocytic lesions thereby expanding the differential diagnosis list. These lesions with oncocytes can be broadly categorized as: oncocytic hyperplasia, oncocytomas, oncocytic variants in other salivary gland neoplasms, and malignant oncocytic tumors. Therefore, the differential diagnosis of OMEC ranges from benign conditions such as oncocytoma, metaplastic Warthin tumor, pleomorphic adenoma with oncocytic change, and to malignancies like oncocytic carcinoma, acinic cell carcinoma and mammary analogue secretory carcinoma. [1,3,4]. Distinguishing these lesions from OMEC is pertinent in view of prognostic differences and management [4].

Diagnosing OMEC can be challenging, particularly if the typical MEC cells are limited to small foci or entirely absent. Pathologists also may overlook OMEC, especially in fine needle aspiration (FNA) samples, due to the presence of numerous other oncocytic lesions affecting the salivary glands. This is particularly true when the predominating oncocytic cells lack nuclear atypia, mitotic activity, or necrosis [2]. However, in this case, the cytology was unsatisfactory in view of cyst contents. In view of overlapping histological features with oncocytoma, oncocytic carcinoma, or other oncocytic neoplasms, the diagnosis of OMEC often requires a thorough sampling, detailed histological examination, immunohistochemical stains, special stains, and potentially advanced techniques such like Fluorescence In Situ Hybridization (FISH) or Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR). One of the key morphological features in distinguishing OMEC is the presence of mucous cells. The identification of these cells able to differentiate it from oncocytosis, oncocytoma, and oncocytic carcinoma [3].

The use of immunohistochemical stains is also paramount for diagnosis. Studies have demonstrated that p63 is a reliable marker for distinguishing OMEC from other tumours. This stain exhibits diffuse nuclear staining in the epidermoid component of OMEC, while oncocytoma and oncocytic carcinomas typically show a peripheral staining pattern [1,2,4]. The expression of p63 or p40 in the absence of SOX 10 or S100 also favours MEC, whereby acinic cell carcinoma and mammary analogue secretary carcinoma have been excluded respectively [5]. PAS-D and mucicarmine stains are helpful in identifying mucin and mucous cells [2,3]. Ki-67 also can be performed to evaluate the mitotic activity [3]. The MSKCC mitotic rate cut off for grading as follows : 0-1/10hpf (low grade), 2-3/10hpf (Intermediate grade), 4 and more /10hpf (high grade). Whereas, the AFIP assigns 3 points for mitotic count of 4 in 10 hpf [5]. Additionally, RT-PCR or FISH can be employed to detect MAML2 translocation since this fusion is quite specific for MEC [1,2,3,4,5]. However, MAML2 translocation has been successfully detected in 66% of typical MEC cases. There has been one case of MAML2 negative OMEC reported in literature, therefore the diagnosis of OMEC should not be solely based on this translocation. The prognostic significance of MAML2 translocation is still debatable [4]. Table 1 illustrates the morphological features, immunohistochemical stains, and molecular studies of differential diagnosis for oncocytic lesions. Table II shows reported cases of oncocytic mucoepidermoid carcinoma along with its morphological features and immunohistochemical stains used in aiding the diagnosis. The three grading systems evaluated by WHO are AFIP, Brandwein and MSKCC, where the latter is a qualitative assessment whereas the remaining two are quantitative. WHO recommends the usage of AFIP in view of its reproducibility, whereby five histological features are assessed namely; architecture (cyst formation), perineural invasion, necrosis, mitosis and nuclear pleomorphism. Brandwein also uses similar categories in addition to presence of invasive border, lymphovascular and bony invasion. Meanwhile, MSKCC only evaluates presence of predominantly solid or cystic component, necrosis, and mitotic count where most of the criterias are not well defined. It was noted that Brandwein tend to upgrade MECs in comparison to AFIP eventhough some low grade tumours with AFIP grading has a tendency to behave more aggressively [5].

Table I: Illustrates the morphological features, immunohistochemical stains and molecular studies of differential diagnosis for oncocytic lesions.

Differential diagnosis of salivary gland oncocytic lesions	Morphology	Immunohistochemistry stains/ Molecular	Features differentiating from OMEC
OMEC	Presence of mucous, intermediate, and epidermoid (squamoid) tumour cells forming cystic and solid growth patterns.	Squamoid and intermediate areas shows diffuse positivity for CK 5/6, p63 and p40 respectively Mucin areas : Mucicarcime positivity and diastase-resistant PAS staining Negative for S100 and SOX 10 Molecular: Usually associated with MAML2 rearrangement	
Oncocytoma	Encapsulated tumour exhibiting an organoid/alveolar growth pattern separated by thin fibrous connective tissue septa	p63, p40 and CK 5/6 basal/peripheral staining	Encapsulation. Absence of mucous, epidermoid, and intermediate cells Negative for mucin stain
Metaplastic Warthin tumour	Papillary cystic lesion with bilayered oncocytic epithelium overlying lymphoid stroma	Metaplastic squamous cell positive for p40, p63 and CK 5/6.	Absence of mucous cells Non infiltrative
Pleomorphic adenoma with oncocytic change	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 (CD117) positive in ductal component	Encapsulation. Chondromyxoid areas and presence of ducts Non infiltrative
Oncocytic carcinoma	Unencapsulated, single, or multinodular tumour. Oncocytic cells exhibit pleomorphism. Infiltration into the salivary gland parenchyma in the form of trabeculae, sheets, and nests	p63, p40 and CK 5/6 basal/peripheral staining	Absence of mucous, epidermoid, and intermediate cells and presence of atypical features. Negative for mucin stains.
Acinic cell carcinoma	Acinic cells that have a granular and basophilic cytoplasm and eccentric located nuclei	Tumour cells are SOX 10 positive	Granular and basophilic cytoplasm
Mammary analogue 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.	Tumour cells are positive for mammoglobin and S100. Intraluminal secretions are PAS positive and PAS-D resistant. Negative for myoepithelial markers p63.	Negative for p63 Molecular: ETV6 translocation

Table II shows reported cases of oncocytic mucoepidermoid carcinoma along with its morphological features and immunohistochemical stains used in aiding the diagnosis.

Year	Clinical history	Cytological diagnosis	Histological diagnosis
2017	43 year old female patient with right palate swelling for 3 years	Not applicable	Low grade oncocytic mucoepidermoid carcinoma (Morphological diagnosis)
2022	67 years old female with left parotid mass (duration not mentioned)	Benign oncocytoma	Oncocytic mucoepidermoid carcinoma. (not graded) Immunohistochemistry: Tumour cells were positive for CK7, with focal basal positivity for CK5/6 and p63. Mucus cells and intraluminal secretions were positive for mucicarmine. Tumour cells were negative for S100, CD10, c-kit.
2019	26 years old male with left jaw mass for 9 months	Not applicable	Intermediate grade oncocytic mucoepidermoid carcinoma. Immunohistochemistry: Tumour cells were positive for CK 5/6, CK7, p63, with weak positivity for CK14. Mucus cells and intraluminal secretions were positive for mucicarmine. Tumour cells were negative for CK20, GCDFP, SOX10, Androgen receptor, GATA3. Ki-67: <10%
2022	73 year old female with left neck mass for 11 months.	Confirmed malignancy (type of lesion not mentioned)	Intermediate grade oncocytic mucoepidermoid carcinoma. Immunohistochemistry: Tumour cells were positive for CK 5/6, p63, p40 with weak positivity for GATA3, GCDFP-15. Mucus cells and intraluminal secretions were positive for mucicarmine. Tumour cells were negative for CK 7, calponin, S100, TTF-1 and thyroglobulin.

CONCLUSION

As with all pathologies, proper sampling of the excised specimen is essential to avoid diagnostic errors that may arise from limited or selective sampling. Given the wide range of differential diagnoses, pathologists should begin by identifying mucous cells, which can help to rule out oncocytoma and oncocytic carcinomas. While most oncocytic lesions are benign, pathologists must always consider the possibility of malignant oncocytic tumors, as clinical management and prognosis vary. Employing ancillary techniques may be valuable in making an accurate differential diagnosis. A thorough histological examination in conjunction with immunohistochemical stains, and other ancillary tests helps to arrive at the accurate diagnosis of OMEC.

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