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Case Report

Unilocular cystic mucoepidermoid carcinoma: 6 cases reported and literature review

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Abstract: Unilocular cystic mucoepidermoid carcinoma (UCMEC) is a rare and diagnostically challenging variant of mucoepidermoid carcinoma, frequently misdiagnosed preoperatively as a benign cystic lesion. We retrospectively analyzed six cases of UCMEC treated between January 2021 and May 2025. The cohort included three males and three females, with a mean age of 55.66 years (range: 24-77). The tumors were located in the parotid gland (n=4) and palate (n=2), with one palatal lesion exhibiting bony extension. The mean maximum tumor diameter was 2.5 cm. Histologically, all cases showed a predominant unilocular cystic architecture. Immunohistochemistry was positive for P40, P63, and CK7, supporting epithelial differentiation. Mucin production was confirmed by Alcian Blue-Periodic Acid Schiff (AB-PAS) staining. According to the AFIP grading system, five cases were low-grade and one was high-grade. Molecular analysis identified MAML2 gene fusion in five cases (83.3%), all of which were low-grade tumors. Surgical resection is the cornerstone of treatment. The detection of MAML2 fusion is a valuable diagnostic and prognostic marker, being strongly associated with low-grade histology and a favorable outcome. This case series aims to elucidate the clinicopathological and molecular characteristics of UCMEC to improve diagnostic accuracy. Accurate preoperative or intraoperative distinction from benign lesions and correct grading are paramount for determining the appropriate surgical scope and optimizing patient prognosis.

Keywords: Unilocular cystic mucoepidermoid carcinoma (UCMEC), salivary gland neoplasms, mainbrain-like gene family 2 (MAML2) gene fusion, prognosis, preoperative diagnosis

Introduction

Mucoepidermoid carcinoma (MEC) is a common malignant salivary gland tumor; however, its unilocular cystic variant is rare [1]. This morphological subtype is frequently misdiagnosed by both clinicians and pathologists, particularly during intraoperative frozen section examination, often due to insufficient sampling or interpretive challenges. Such diagnostic errors may lead to inadequate surgical management and pose significant risks to patient safety. Due to the considerable heterogeneity in the pathological presentation of MEC, accurate grading remains challenging. The Armed Forces Institute of Pathology (AFIP) grading system demonstrates improved identification of cases with unfavorable prognosis and is particularly suitable for classifying unilocular cystic MEC [2]. Based on a scoring system that evaluates five histological parameters-cystic component, perineural infiltration, necrosis, mitotic activity, and anaplasia, tumors are categorized as low, intermediate, or high grade.

In this study, fluorescence in situ hybridization (FISH) was used to detect MAML2 gene fusion in unilocular cystic mucoepidermoid carcinoma (UCMEC). The creb-regulated transcriptional coactivator 1 (CRTC1) - mainbrain-like gene family 2 (MAML2) translocation, detected in 33.7-85.5% of MECs, results in MAML2 gene rearrangement on chromosome 11 and MAML2 fusion with CRTC1 on chromosome 19. Gene fusion is usually detected in low-intermediate grade unilocular cystic lesions and is often negative in high-grade cases, which may indicate a poor prognosis of the disease.

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Due to the lack of specific and representative clinical symptoms and epidemiological features, accurate diagnosis of UCMEC relies on the integration of clinical presentation, histopathological evaluation, immunohistochemistry (IHC), and fusion gene analysis. Fewer than 30 cases of UCMEC have been reported in the literature to date [1]. This study retrospectively analyzes six additional cases of UCMEC to contribute to a more comprehensive understanding of this rare variant of mucoepidermoid carcinoma.

Case presentation

Case selection and follow-up

This study was approved by the Ethics Review Committee of Lu'an Hospital Affiliated with Anhui Medical University. Six cases of unilocular cystic mucoepidermoid carcinoma diagnosed between January 2021 and May 2025 were retrieved from the pathology database. All hematoxylin-eosin (HE) and immunohistochemical slides were re-evaluated and graded by senior pathologists.

Clinical data, including age, gender, chief complaint, tumor location, imaging findings, surgical approach, and treatment details, were collected from the electronic medical record system. All patients underwent regular follow-up.

Histology and immunohistochemistry

AB-PAS staining: The reagent kit (BA4121; BESO, Zhuhai) was performed according to the manufacturer's instructions. Briefly, sections were deparaffinized routinely, incubated with alcian blue solution for 15 minutes, treated with periodic acid solution for 10 minutes, and rinsed with distilled water. This was followed by staining with Schiff's reagent for 10-15 minutes and counterstaining with hematoxylin for 3 minutes. Finally, sections were rinsed under running water for 3-5 minutes, dehydrated, cleared, and mounted with neutral gum.

Immunohistochemical (IHC) staining: Antigen retrieval was performed under high pressure using citric acid buffer. Sections were then incubated with an endogenous peroxidase blocker for 10 minutes and washed three times with PBS (3 minutes each). Subsequently, they were incubated with primary antibody at 37°C for 60 minutes, followed by treatment with an enzyme-labeled polymer at 37°C for 30 minutes. Chromogenic development was carried out using DAB for 3-5 minutes. Finally, sections were dehydrated, cleared, and sealed. Positive and negative controls were included in each run. All primary antibodies were ready-to-use and purchased from Maxim, China: CK5/6 (MAB-0744), P40 (RMA-1006), P63 (MAB-0694), Ki-67 (MAB-0672), and Calponin (MAB-0712).

Fluorescence in situ hybridization (FISH)

FISH was performed using a break-apart probe targeting the MAML2 gene locus (Anbiping, Guangzhou). All procedures were conducted in strict accordance with the manufacturer's protocol.

Results

Clinicopathological features

A total of six patients with unilocular cystic mucoepidermoid carcinoma (UCMEC) in the head and neck region were included in this analysis. All patients presented with space-occupying lesions and localized swelling. The cohort consisted of three males (50%) and three females (50%), with ages ranging from 24 to 77 years (mean age: 55.66 years). The mean maximum tumor diameter was 2.5 cm. Tumors were located in the parotid gland in four cases (66.7%) and in the palate in two cases (33.3%), one of which involved the alveolar bone and maxillary sinus floor. All lesions were cystic, unencapsulated, and exhibited ill-defined borders with adjacent tissues. Cystic contents were described as follows: absent in two cases, mucoid in two, gelatinous in one, and purulent in one. Based on AFIP grading criteria, five cases were classified as low-grade and one as high-grade by experienced pathologists. Fluorescence in situ hybridization (FISH) analysis detected MAML2 gene fusion positivity in five cases and negativity in one (**Table 1**).

Imaging features

All patients underwent preoperative imaging (ultrasonography or computed tomography), which revealed cystic masses with maximum diameters ranging from 1.5 cm to 5.0 cm

Table 1. The basic clinical characteristics of the lesion and the results of MAML2 rearrangement

Case	Age	Gender	Location of lesion	Tumor size	AFIP classification	Contents of capsule	MAML2 fusion
1	41	M	Right Parotid gland	2.2×1.8×1.5 cm	Low grade	Loss of content	positive
2	61	M	Left maxillary region, proximal left maxillary alveolar bone and maxillary sinus floor	1.5×1.0×1.0 cm	Low grade	Purulent contents	positive
3	75	F	Right upper jaw with right upper molar	2.0×1.5×0.5 cm	Low grade	Mucoid contents	positive
4	56	M	Right retroauricular parotid gland	2.8×2.3×1.3 cm	Low grade	Mucoid contents	positive
5	77	F	Left retroauricular parotid gland	5.0×2.2×1.6 cm	Low grade	Loss of content	positive
6	24	F	Left parotid gland	1.5×1.5×0.8 cm	High grade	Gelatinous contents	negative

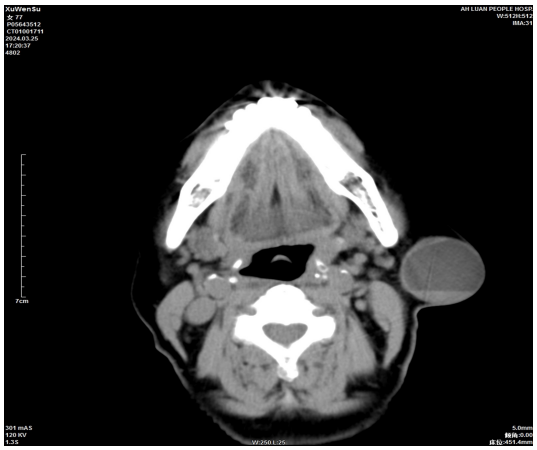

Figure 1. CT scan demonstrating a well-demarcated cystic mass in the retroauricular parotid gland region.

(mean: 2.5 cm). Tumor margins were poorly defined. Case 2 showed bone compression and resorptive changes along the floor of the maxillary sinus. Among the cases, Case 4 was initially diagnosed as pleomorphic adenoma of the parotid gland, and Case 5 as a retroauricular sebaceous cyst. The remaining four cases lacked a definitive preoperative diagnosis (**Figure 1**).

Pathological examination

The imaging and clinical manifestations of these cystic lesions were not indicative of malignancy, rendering intraoperative frozen section diagnosis challenging for pathologists. Microscopic examination revealed that the cystic walls consisted of collagen fibers accompanied by solid cell nests, microcysts, and mucin-containing goblet cells. Mucin production was confirmed by Alcian Blue-Periodic Acid-Schiff (AB-PAS) staining. Some well-differentiated epidermoid cells exhibited lightly stained cytoplasm; differential diagnoses included squamous metaplasia of ductal columnar epithelium, clear cell carcinoma, and secretory carcinoma of the salivary gland. Immunohistochemically, P40/P63 positivity supported epidermoid and intermediate cells, while CK7 indicated glandular epithelial differentiation. The absence of DOG-1 and CD117 expression helped exclude adenoid cystic carcinoma. Similarly, negative staining for AACT and S-100 aided in ruling out acinar cell carcinoma. The cell proliferation index was low in all cases (approximately 5%). Negative surgical margins were confirmed in all except Case 5, where margin assessment during frozen section was hampered by tissue fragmentation. Subsequent evaluation of pericapsular salivary gland tissue confirmed complete tumor excision. Adjacent salivary gland tissue exhibited chronic inflammation and stromal collagen fiber hyperplasia, likely secondary to tumor stimulation (**Figure 2**).

Molecular testing

MAML2 gene fusion was detected in five out of the six cases (83.3%). Representative FISH images are provided below (**Figure 3**). The 5' MAML2 (11q21) probe was labeled with red fluorescence, and the 3' MAML2 probe was labeled with green fluorescence, and the normal mode was 2F (Note: F is yellow signal or red and green superimposed signal). A total of 200 tumor cells were counted and percent split signal was recorded (>7% were positive, MAML2 gene rearrangement).

Treatment and follow-up

All patients were treated with complete surgical excision and did not receive adjuvant therapy. During the follow-up period, none of the patients developed local recurrence or distant metastasis.

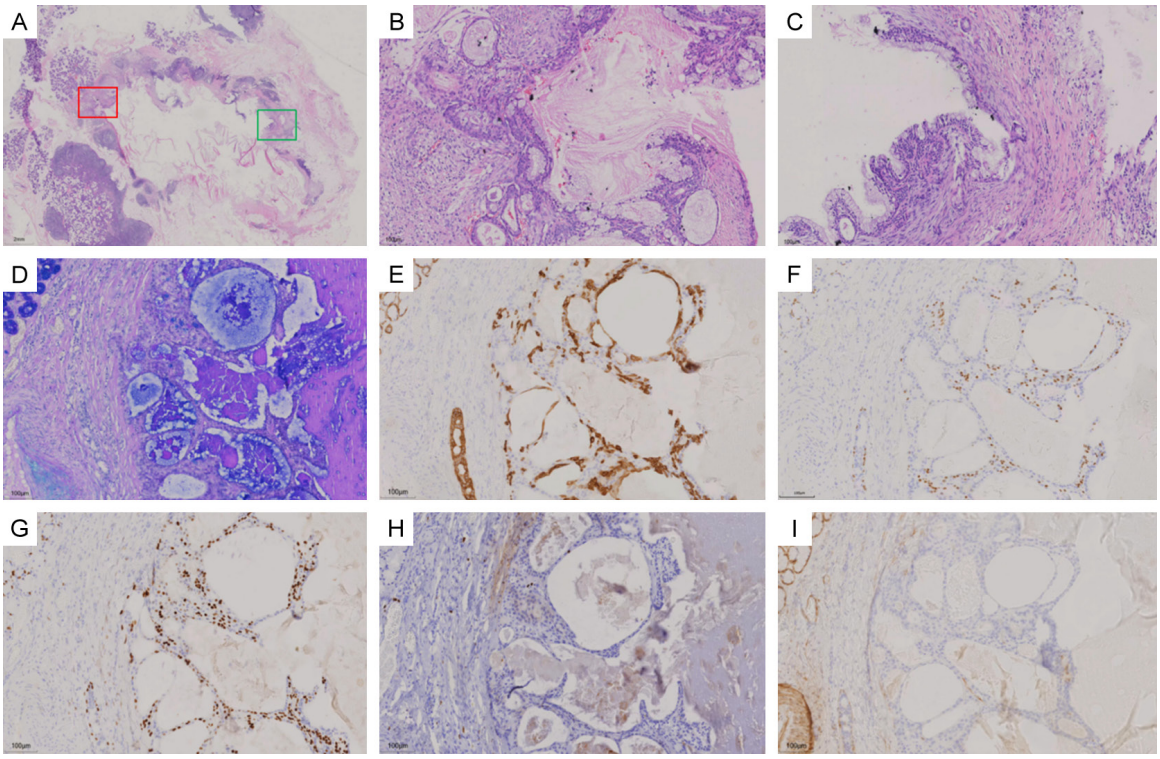

Figure 2. Hematoxylinandeosin (HE) staining and immunohistochemical staining (Alcian Blue-Periodic Acid-Schiff staining and Immunohistochemistry staining) showing tumor tissue morphology and immunophenotype. (A) Hematoxylinandeosin (HE) staining shows the lesion was a solitary cystic structure (HE×10, scale bar: 2 mm). (B, C) Hematoxylinandeosin (HE) staining shows a magnified view of the inner wall of the sac (HE×200, scale bar: 100 μm; (B) corresponds to the red box and (C) corresponds to the green box in (A). (D) Alcian Blue-Periodic Acid-Schiff staining (AB-PAS×200, scale bar: 100 μm) shows the mucin-producing cell components. (E-I) Immunohistochemistry staining (IHC×200, scale bar: 100 μm) show expression of markers: (E) CK5/6 (cytokeratin 5/6) positive with tumor cells; (F) P40 positive with tumor cells; (G) P63 positive with tumor cells; (H) KI67 positive with tumor cells; (I) Calponin positive with tumor cells.

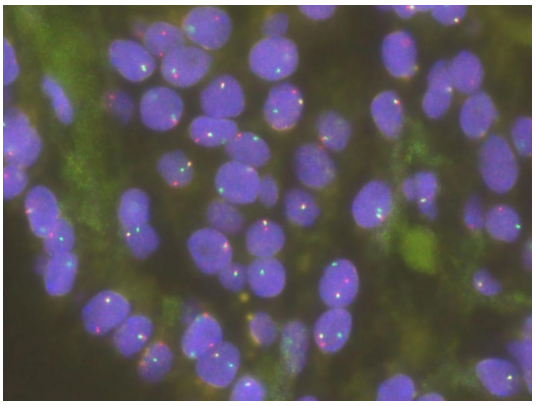

Figure 3. FISH shows the molecular characteristics of unilocular cystic mucoepidermoid carcinoma: MAML-2 fusion positive (FISH×1000, objective lens 100×, eyepiece 10×).

Discussion

Unilocular cystic mucoepidermoid carcinoma (UCMEC) represents an uncommon histopathological variant, comprising approximately 2.4% of all MECs [3]. Its deceptively benign radiographic and macroscopic appearance frequently leads to diagnostic inaccuracies among clinicians, radiologists, and pathologists. Typical clinical manifestations include localized swelling or a palpable mass. Conventional imaging often demonstrates a unilocular cystic architecture with variably demarcated boundaries. Fine-needle aspiration cytology exhibits limited diagnostic efficacy (sensitivity ≈70%), attributable to inadequate cellular sampling and dilutional artifacts from cystic fluid [4]. Consequently, intraoperative distinction between benign cystic entities and unilocular cystic MEC remains challenging, particularly during frozen section analysis, where margin assessment is of paramount importance.

Histopathological examination reveals a characteristic triphasic cellular composition: epidermoid cells, mucin-producing goblet cells with

vacuolated cytoplasm, and intermediate cells. Prominent keratinization in epidermoid cells may simulate squamous metaplasia of ductal epithelium. Mucinous differentiation is often subtle in frozen sections, manifesting as faint basophilic cytoplasmic stippling. When mucoepidermoid carcinoma is suspected intraoperatively, definitive diagnosis requires paraffin sections with AB-PAS histochemical staining to confirm mucin production. Well-differentiated tumors may demonstrate clear cell changes and intricate admixture of epidermoid and mucinous elements, necessitating differential diagnosis from acinic cell carcinoma, secretory carcinoma, and adenosquamous carcinoma [5, 6].

MECs are histologically stratified into low and high grade categories based on the proportion of cellular components. Low-grade tumors exhibit predominant mucinous and epidermoid differentiation, whereas high-grade neoplasms are composed chiefly of epidermoid and intermediate cells with minimal mucinous elements (<10%). Our cohort included five low-grade and one high-grade case. Furthermore, cystic MEC has been subclassified by Xi Wang [1] into two morphological patterns: Type A denotes a pure cystic structure with/intraluminal nodules, and Type B displays invasive tumor clusters within the cyst wall or fibrous stroma. Our series contained two Type A and four Type B cases.

The CRTC1/MAML2 gene fusion is a molecular hallmark of MEC, implicated in oncogenic pathogenesis [3], with a reported incidence of 78% [2]. This translocation is more prevalent in low-grade tumors [7], and its absence in advanced-stage (>T2) or high-grade (G3) lesions correlates with adverse clinical outcomes [8]. While some studies propose CRTC1-MAML2 as a favorable prognostic indicator [9], a multi-institutional analysis of 454 MECs found no significant association between MAML2 status and tumor grade, survival, or prognosis [3]. Alternative genetic alterations, such as BAP1 mutations, may drive aggressive phenotypic evolution. In our cohort, MAML2 rearrangement was detected in 83.3% (5/6) of cases, all of which were low-grade; the single fusion-negative case was high-grade. These observations align with existing literature. Negative MAML2 status may reflect technical limitations of FISH or genuine biological heterogeneity [10]. Given the rarity of unilocular cystic MEC, our findings contribute to the molecular characterization of this variant. Further longitudinal studies are warranted to elucidate the prognostic implications of MAML2 fusion status.

Surgical resection with histologically negative margins constitutes the primary therapeutic intervention. Incomplete excision often stems from diagnostic ambiguity during preoperative and intraoperative evaluations. The majority of unilocular cystic MECs are low-grade malignancies, exhibiting a 5-year survival rate of 90-100% and a recurrence rate of 8.5% [11]. Structured follow-up is indicated for patients with clear margins. For recurrent or high-grade tumors, immune checkpoint inhibitors (e.g., anti-PD1, anti-PDL1, anti-CTLA4) represent emerging therapeutic options, though clinical evidence remains limited [12]. Additional investigational approaches include androgen deprivation and anti-HER2 targeted therapies [13].

This study has several limitations, including its retrospective single-center design and the intrinsic rarity of unilocular cystic MEC. Diagnostic evolution over time and technical constraints historically limited case identification. Furthermore, the extended recruitment period necessitates ongoing follow-up for comprehensive survival analysis. Nevertheless, our clinicopathological and molecular analysis of six cases enhances understanding of this entity among diagnosticians and surgeons. These findings underscore the importance of recognizing the malignant potential of cystic salivary lesions and achieving clear surgical margins. Given the predominantly indolent behavior of low-grade unilocular cystic MEC, conservative resection with vigilant monitoring is generally sufficient to avoid overtreatment, except in high-grade variants.

Conclusion

Accurately identifying UCMEC and avoiding misdiagnosis as a benign cyst is critically important yet challenging. Surgical resection remains the primary treatment option. The presence of MAML2 gene fusion is indicative of a favorable prognosis. Early and accurate differentiation between benign and malignant lesions, along with an assessment of the malignancy grade, critically influences the extent of surgery, choice

of therapeutic strategy, and overall patient prognosis.

Disclosure of conflict of interest

None.

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