

# INTRA-CYSTIC (IN SITU) MUCOEPIDERMOID CARCINOMA: A CLINICO-PATHOLOGICAL STUDY OF 14 CASES

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**Running head:** Intra-cystic mucoepidermoid carcinoma

## Abstract

**Aims:** To report on the clinico-pathological features of a series of 12 intra-oral mucoepidermoid carcinomas showing exclusive intra-cystic growth.

**Methods and methods:** All mucoepidermoid carcinomas diagnosed in the period 1990-2012 were retrieved, the original histological preparations were reviewed to confirm the diagnosis, and from selected cases, showing exclusive intra-cystic neoplastic component, additional sections were cut

at 3 subsequent 200  $\mu$ m intervals and stained with Hematoxylin-Eosin, PAS and Alcian Blue, to possibly identify tumor invasion of the adjacent tissues, which could have been overlooked in the original histological preparations. Also, pertinent findings collected from the clinical charts and follow-up data were analyzed.

**Results:** We identified 14 intraoral mucoepidermoid carcinomas treated by conservative surgery and with a minimum follow up of 5 years. The neoplasm were located in the hard palate (9 cases), the soft palate (2), the cheek (2) and the retromolar trigone (1). In all instances histological examination was revealed the presence of a single cystic space, containing clusters of columnar, intermediate, epidermoid, clear and mucous-producing cells, the latter exhibiting distinct intracytoplasmic mucin production, as confirmed by PAS and Alcian Blue stains. The cysts were entirely circumscribed by fibrous connective tissue and no solid areas or infiltrating tumour clusters were detected. Conservative surgical resection was performed in all cases and no recurrences or nodal metastases were observed during the follow up period.

**Conclusions:** Mucoepidermoid carcinomas showing prominent (>20%) intra-cystic proliferation currently are considered low-grade tumours. In addition, we also unveil the possibility that mucoepidermoid carcinomas, at least in their early growth phase, may display an exclusive intracystic fashion and might be considered as in situ carcinomas, unable to infiltrate adjacent tissues or metastasize.

**KEY WORDS:** salivary glands, minor salivary glands, salivary gland carcinoma, mucoepidermoid carcinoma, in situ carcinoma, intra-cystic carcinoma

## INTRODUCTION

Mucoepidermoid carcinoma (MEC) was firstly described by Volkmann in 1895; subsequently, Stewart et al (1945) defined such lesion “mucoepidermoid tumor” and identified tumors with “relatively favorable” and “highly unfavorable” clinical outcome. Subsequently, Jakobsson et al. and many other authors<sup>1-4</sup> proposed to separate MECs into low, intermediate and high grade based on the relative proportion of cell types, a distinction that still persisted in the WHO classification of tumors of 2017.<sup>5</sup> MEC is one of the most common salivary gland malignancies showing distinctive morphological features, such as mucous, intermediate and epidermoid cells in variable proportions<sup>5-7</sup>. Less than half of the cases arise in minor salivary glands, the palate being the most common intra-oral localization of MEC.<sup>8-12</sup> The architectural configuration of MEC may vary but a cystic component is commonly present and sometimes may predominate.<sup>5,6,13-15</sup> Nevertheless, most MECs also show a solid growth pattern and infiltration of adjacent structures.<sup>16,17</sup>

Though considered a tumor with low malignant potential in most instances, about 10% of the patients affected by MEC experience tumor-related death.<sup>10,11,18,19</sup> At this regard, MECs located in the submandibular gland and those showing high histopathologic grade are considered more aggressive.<sup>8-10,20,21</sup> It should be noticed that the greater extension of the intra-cystic component correlates with lower grade of MEC and, therefore, this tumor characteristic “*per se*” may influence the clinical outcome.<sup>5-8,18,19,22</sup>

Based on these premises, while retrospectively re-evaluating all MEC cases examined in the period 1990-2012, we focused our attention on those cases showing prevalent/exclusive intra-cystic component to further characterize its relevance in the clinic-pathological presentation and clinical outcome of the affected patients.

## **MATERIALS AND METHODS**

All cases diagnosed as MEC at our Institution during the years 1990-2012 were retrieved from the files of the Section of Pathological Anatomy of the University of Bari Aldo Moro, along with the pertinent clinical charts and follow-up data updated to January 2019. All cases had been fixed in 10% neutral buffered formalin, embedded in paraffin and routinely stained with Hematoxylin-Eosin, Periodic Acid – Schiff (PAS), with and without diastase treatment, Mucicarmine and Alcian Blue. The original histological preparations were reviewed to confirm the diagnosis, based on the occurrence of the distinct cell types (squamous, mucous-producing and intermediate cells) that characterize MEC.<sup>5</sup> Additional sections at 3 subsequent 200µm intervals were cut of selected cases showing exclusive tumoral intra-cystic component and stained with the above procedures to possibly identify tumor invasion of the adjacent tissues that could have been overlooked in the original histological preparations.

This study was carried out in accordance with the code of ethics of the world medical association (Declaration of Helsinki) and approved by internal ethical committee (study number 4652, prot. 66/C.E). Patients released informed consent on diagnostic and therapeutic procedures and for the possible use of biological samples for research purposes.

## **RESULTS**

During the observational period, 14 MECs were identified as showing an exclusive intra-cystic tumoral component in the absence of infiltration of the adjacent tissues, as confirmed by the evaluation of additional cutting levels, the salient clinico-pathological features of which are reported in Table 1. Among such patients there were 3 males and 11 females, with a median age of 36.8 years; 9 MECs involved the hard palate, 2 cases the soft palate, 2 the cheek mucosa and 1 case the retromolar trigone. In all instances, the neoplasms appeared as intra-oral nodules (Fig. 1),

sometimes with slight erosion/ulceration of the surface epithelium, showed painless slow growth, hard consistency, without evident infiltration of the adjacent soft and hard tissues, as confirmed by MR and CT scans. The tumor dimensions were relatively small, with a minimum clinical diameter of 0,5 mm up to a maximum of 1,8 mm. No loco-regional node involvement was detectable in all instances. All patients underwent conservative surgical excision with a rim of normal tissue.

Gross examination disclosed well defined cystic lesions and microscopically, at scanning magnification, a single cystic space was detectable in all samples, showing parietal proliferation of clusters of epithelial cells with focal cribriform growth pattern (Fig. 2). The central part of the cyst was filled with proteinaceous material and cholesterol crystals, while a distinct and complete rim of collagenous stroma separated the cyst from the surface epithelium and from adjacent lobules of mucous salivary glands. The clusters of epithelial proliferation (Fig. 3) were composed by small columnar and intermediate cells, cells with prominent cytoplasmic clearing and margined nuclei, scattered flat to polygonal cells showing epidermoid differentiation and a reduced number of large mucous-producing cells with multivacuolated cytoplasm. The latter were better highlighted with Alcian Blue (Fig. 4) and Mucicarmine stains and also showed PAS-positivity, which was partly abolished after diastase treatment. Occasionally, smaller cystic spaces with cribriform appearance were evident within the neoplastic epithelial clusters, which were lined by cuboidal to columnar cells. Nuclear pleomorphism was minimal, as was mitotic activity (<1/10 high power fields), while inflammatory infiltration, necrosis and perineural invasion were undetectable; also, tumor-free margins were assessed in all cases. Patients had been followed-up for a minimum of 5 years and had remained without evidence of disease up to January 2019.

## DISCUSSION

Salivary gland carcinomas represent about the 5% of all head and neck carcinomas and the 0,5% of all malignancies,<sup>5,8-10,24-26</sup> with an incidence of 1.1 in 100,000 per year in the Caucasian population<sup>9,26-28</sup> and have been classified into 20 different types by the World Health Organization in 2017.<sup>5</sup>

MEC is the most common malignant tumor of the salivary glands (12–29%) in children and young adults<sup>9,26,29,30</sup> and, according to some authors, the most common malignancy in minor salivary glands:<sup>8-13,20</sup> its peak of incidence is between the third and sixth decade but it is one of the most salivary malignancies that may occur in children and adolescent under 20 years of age with predilection for women.<sup>26,29,30</sup> As confirmed by the results of the present study, the palate remains the most commonly involved site by MECs occurring in minor salivary glands, while they less frequently occur in the retromolar area, the floor of the mouth, the buccal mucosa, the lips and the tongue.<sup>3,5,18,24</sup>

The cases reported herewith showed the distinctive morphological features of “classical” MEC<sup>5,31,32</sup> i.e., an epithelial tumor composed by intermediate, epidermoid, mucous-producing and clear cells, arranged in irregular clusters of variable size but, at variance with conventional MEC, no foci of stromal invasion were detected and the neoplastic proliferation manifested an exclusive intracystic growth.

Traditionally, MEC is considered a tumor with low malignant potential, though cases showing local recurrence, nodal and distant metastases and tumor-related death have been repeatedly reported.<sup>8,9,14,17,19,28</sup> Tumor aggressiveness is strictly related to histological grade and, although there is not complete agreement on the grading systems proposed so far, a 3-tiered scale considering low, intermediate and high grade MEC is most commonly adopted and was proven useful for

prognostic purposes.<sup>5,6,13,26,32</sup> Such systems take into account the extension of the intra-cystic component, presence of neural invasion and necrosis, mitotic index and cellular anaplasia.<sup>12,14,15,23,32</sup> At this regard, the cases of the present series, while fitting into the morphological diagnosis of “conventional” MEC, did show but minimal nuclear pleomorphism and occasional, if any, mitotic figures, in the absence of perineural/bone invasion and necrosis, thus qualifying as low grade tumors, with indolent clinical behavior. Herewith, we provide morphological evidence to postulate that a less aggressive form of MEC may be identified, as for epithelial tumors occurring in other organs (e.g., breast and prostate), which could be considered an *in situ* carcinoma. This novel tumor subtype, characterized by exclusive intra-cystic growth, should be, by definition, incapable of infiltrating adjacent tissues and giving rise to nodal or distant metastases and, therefore, easily curable with conservative surgery.

Furthermore, based on the classical morphological features of MEC, intraductal papilloma, cystadenoma, adenosquamous carcinoma, salivary duct carcinoma and salivary gland clear cell carcinomas could have been considered in the differential diagnosis.<sup>21-23,31,32</sup> The lack of any papillary growth pattern and the presence of distinct and frequently prevalent clusters of intermediate cells help to rule out intraductal papilloma and cystadenoma, respectively. Adenosquamous carcinoma and salivary duct carcinoma may closely mimic MEC but such tumor types are devoid of intermediate cells and usually show higher degrees of cellular pleomorphism and mitotic activity. In addition, evident mucin production within the neoplastic cells contributes to exclude other types of salivary gland carcinomas with clear cells (e.g., acinic cell carcinoma, hyalinizing carcinoma) that also lack of an intermediate cell population.<sup>14,22,234</sup>

It is well known that MECs may harbor MAML2 gene fusion but, in view of the typical morphologic features of all case of the present series, we considered further assessment of the status of MAML2 would have not added much to this study. In fact, it is generally accepted that up to

75-80% of MECs, especially low- and intermediate grade, harbor gene fusions involving MAML2<sup>33-36</sup> Despite the high specificity, MAML2 testing is no longer believed a useful prognostic factor for already diagnosed MEC and frequently overlooked when the diagnosis of MEC is reached straightforward.<sup>34,35,37</sup> The role of MAML2 testing as ancillary diagnostic adjunct is still reserved for MEC showing un-conventional histological appearances.<sup>38,39</sup> In fact, the finding of a MAML2 rearrangement is useful in distinguishing the oncocytic variant of MEC from oncocytoma and oncocytic carcinoma, the Whartin-like variant and, additionally, a recently described new variant defined as ciliated, showing the presence of ciliated cell classically detectable in benign developmental cyst and also in the recently recognized ciliated HPV-related squamous cell carcinoma.<sup>40,41</sup>

In addition, we would also like to emphasize that we were unable to identify MEC with exclusive intra-cystic (in situ) growth in major salivary glands but this may be related to higher chances to detect such tumors at an earlier growth phase when located in intra-oral sites, in view of easier accessibility to inspection and palpation. In other words, we cannot exclude that intra-cystic (in situ) MEC may be present in major salivary glands but, possibly, they remain undetected for longer times and are disclosed when infiltration of adjacent tissues has already occurred.

Finally, the pathogenesis of malignant salivary gland neoplasms, as well as the occurrence of genetic and epigenetic alterations remain still unclear. However, it would be interesting to explore whether the typical chromosomal translocation t(11;19) (MECT1-MAML2), which is detected in >50% of “conventional” MEC, is already present in tumors at such an early stage of tumorigenesis such as those of the present series and if additional genetic alterations might be responsible for further progression to frankly invasive MEC.

## AUTHOR DISCLOSURE STATEMENT

No competing financial interests exist.

## FUNDING INFORMATION

No funds are declared for this study.

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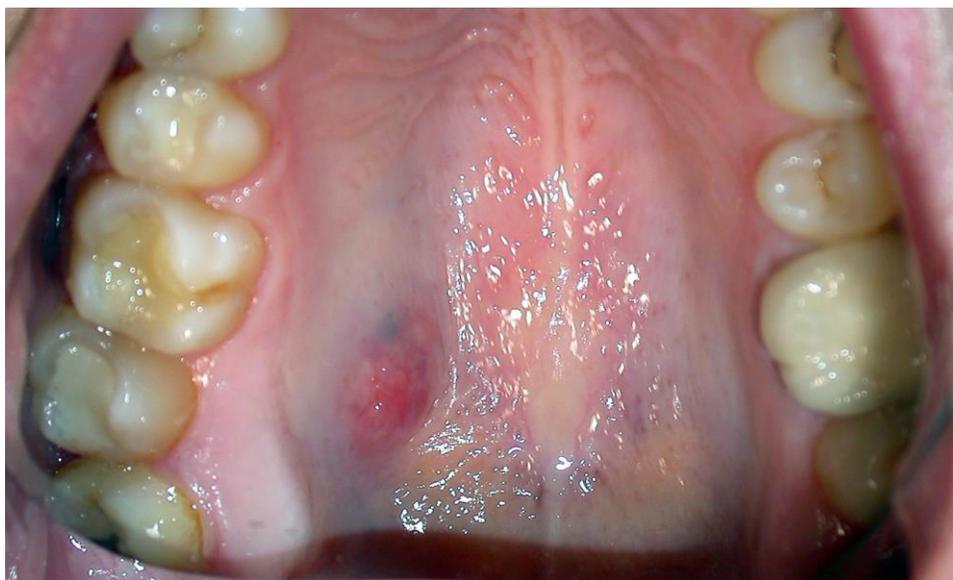
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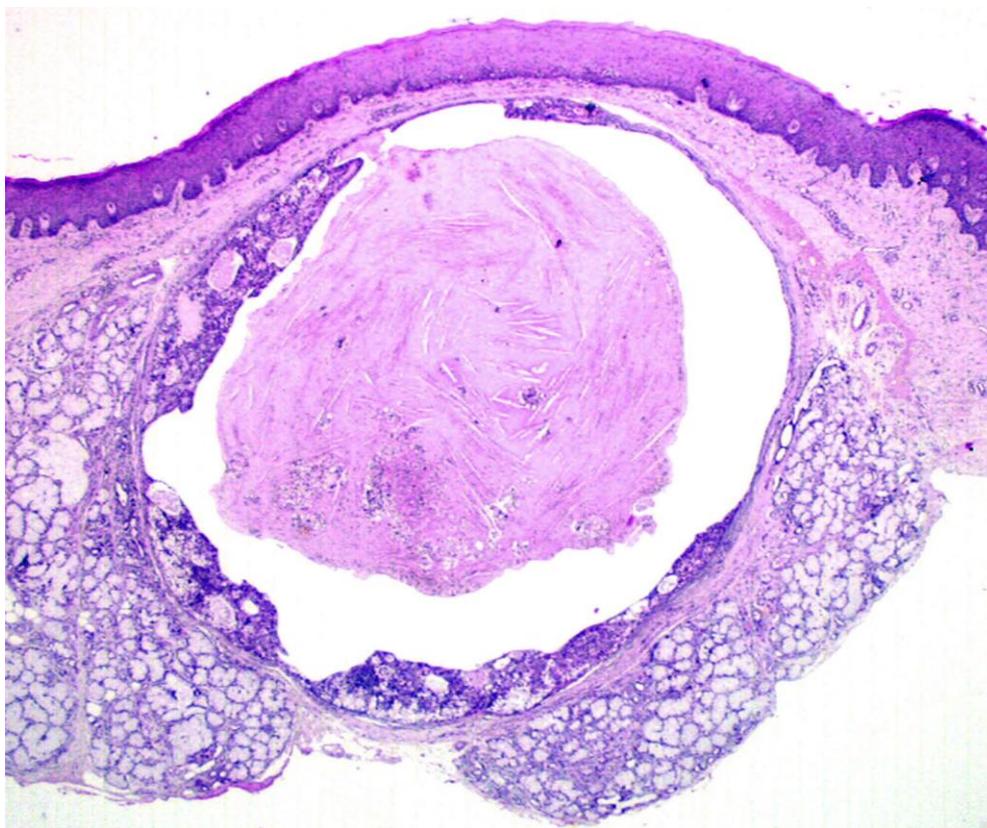
**Table 1:** Clinico-pathological features of the patients with intra-cystic mucoepidermoid carcinoma (all alive without evidence of disease after the specified follow-up interval)

Case #	Age	Sex	Site	Size (cm)	Follow-up (months)
1	51	F	Hard palate	0,6	66
2	26	F	Hard palate	1,8	62
3	20	M	Soft palate	1,3	88
4	25	F	Hard palate	0,7	74
5	36	F	Hard palate	0,5	84
6	35	F	Cheek	0,9	68
7	34	F	Hard Palate	1,0	74
8	41	F	Cheek	1,2	62
9	28	M	Soft palate	0,8	68
10	46	F	Hard palate	1,1	62
11	50	M	Hard palate	1,8	120
12	39	F	Hard palate	1,2	95
13	45	F	Retromolar trigone	1,6	66
14	40	F	Hard palate	1,2	68

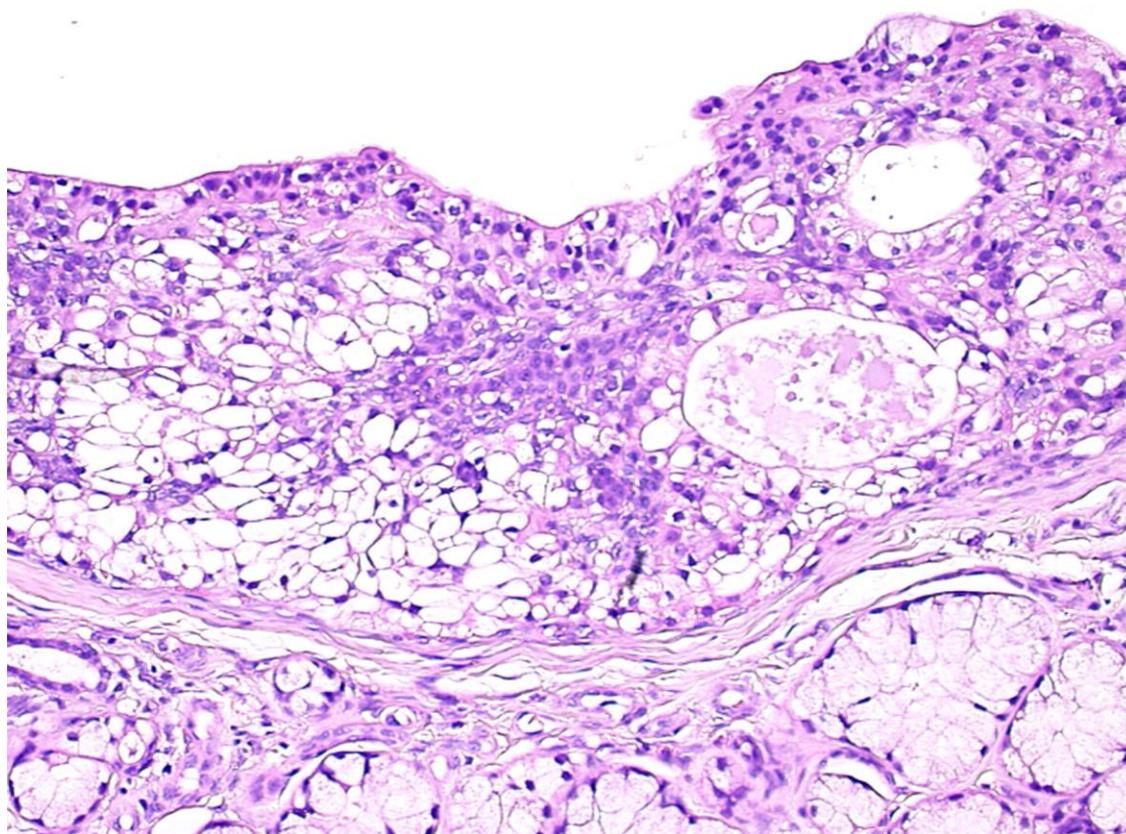
## FIGURE LEGENDS



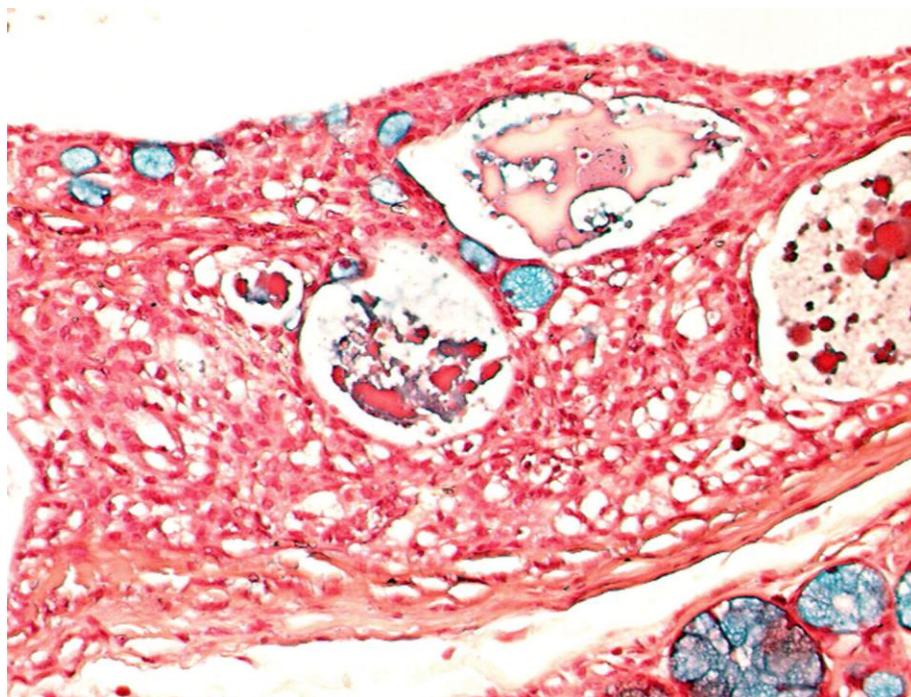
**Figure 1:** Clinical presentation MEC of the hard palate as a rather well demarcated nodule with slight erosion of the covering mucosa.



**Figure 2:** At scanning magnification, the tumor was composed by a single cystic space, partly filled with proteinaceous material and cholesterol crystals, showing parietal growth of epithelial cells and complete peripheral demarcation by fibrous connective tissue. (H&E, x1)



**Figure 3:** The epithelial component consisted in small columnar and intermediate cells, cells with prominent cytoplasmic clearing, rare flat to polygonal cells showing epidermoid differentiation and a reduced number of large mucous-producing cells with multivacuolated cytoplasm. (H&E, x10)



**Figure 4:** Epithelial cells with multi-vacuolated cytoplasm and marginated nuclei demonstrate consistent Alcian Blue positivity indicating mucous production. (Alcian Blue, x20)