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ORIGINAL PAPER

# Glandular Odontogenic Cysts (GOCs) Lack *MAML2* Rearrangements: A Finding to Discredit the Putative Nature of GOC as a Precursor to Central Mucoepidermoid Carcinoma

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**Abstract** Glandular odontogenic cyst (GOC) is a cyst of the gnathic bones that is characterized by squamous and glandular differentiation. The histopathologic features of GOC overlap considerably with central mucoepidermoid carcinoma (MEC), suggesting that GOC could be a precursor lesion to, or even a low-grade form of, central MEC. Differentiating the two lesions may be difficult or impossible on a limited biopsy. *MAML2* rearrangements have been recently found to be specific for MEC, even those arising in the jaws. An analysis of *MAML2* in GOCs could help clarify its relationship with central MEC. Tissue blocks from 21 GOCs and 5 central MECs were retrieved from the surgical pathology archives of The Johns Hopkins Hospital. Each MEC exhibited solid areas and clear-cut stromal invasion. In addition, 4 of the MECs demonstrated cystic areas that were histologically similar to GOC. Break-apart fluorescence in situ hybridization for *MAML2* was performed. For the MECs, analysis was performed on both the solid components and the cystic areas that resembled GOC. *MAML2* rearrangements were identified in all 5 of the MECs, but in none of the 21 GOCs (100 vs. 0 %; $p < 0.0001$, Fisher's Exact). In the MECs, the rearrangement was present in both the solid and GOC-like cystic areas. While central MECs consistently harbor the *MAML2* rearrangement, even in low-grade cystic areas that resemble a pre-existing GOC, true GOCs do not. Accordingly, GOC does not appear to represent an early or low-grade form of central MEC, but rather an unrelated lesion. The high sensitivity and specificity of *MAML2* rearrangement for MECs points to its utility as a diagnostic adjunct in separating mucinous cystic lesions of the gnathic bones.

**Keywords** Glandular odontogenic cyst · Central mucoepidermoid carcinoma · *MAML2*

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## Introduction

Central (i.e., primary intraosseous) mucoepidermoid carcinoma (MEC) is a rare malignant neoplasm of the jaws that is identical in most respects to MEC of the salivary glands, but arises entirely within bone [1–5]. Glandular odontogenic cyst (GOC) is an uncommon benign cystic lesion of the gnathic bones initially described in 1987 as "sialo-odontogenic cyst" or "mucoepidermoid odontogenic cyst." [6–16] Since its first description, many investigators have recognized that GOC shares many histologic features with central MEC [1, 2, 5, 7, 9, 10, 16–20]. Indeed, it is common to see areas indistinguishable from GOC within a central MEC [2]. Conversely, "MEC-like" areas within the walls of GOCs have been described [10].

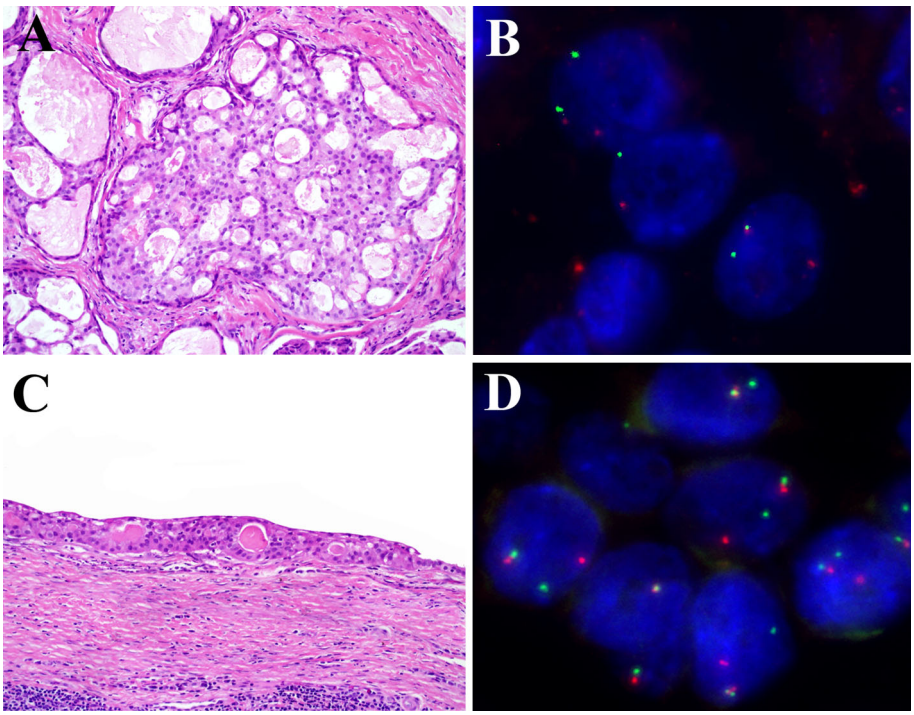


**Fig. 1** In this case of central mucoepidermoid carcinoma, the solid areas of clear cut invasive tumor (**a**) were positive for the *MAML2* rearrangement by break apart FISH (**b**). In very cystic areas of the tumor that mimicked glandular odontogenic cyst (**c**), the translocation was also present (**d**)

These morphologic similarities have prompted speculation that the GOC represents a precursor to, or even a low-grade form of, central MEC [2, 18, 19]. Although not always easy on morphologic grounds, distinguishing GOC from central MEC is important because MECs have a higher rate of recurrence, carry a potential to metastasize to regional lymph nodes, and can in some cases be lethal [1, 4, 5, 21, 22].

Rearrangements of *MAML2* have recently been detected in up to 75 % of MECs of salivary glands, and are very specific for this tumor type [23–27]. They preferentially occur in low/intermediate grade MECs with favorable prognosis where they are regarded as an early genetic alteration that drives tumorigenesis [28]. *MAML2* rearrangements have been reported in two of three central MECs [29, 30], but the *MAML2* status of GOC is not known. We sought to clarify the relationship of GOC to central MEC by performing *MAML2* molecular analysis on these lesions.

## Methods

### Cases

The surgical pathology archives of The Johns Hopkins Hospital were searched for cases of GOC and central (i.e., primary intraosseous) MEC. Slides and tissue blocks from 21 GOCs and 5 central MECs were retrieved. Hematoxylin and eosin-stained sections were reviewed to confirm the diagnoses. Each MEC exhibited solid areas and clear-cut stromal invasion. In addition, four of the MECs demonstrated focal cystic areas that were histologically similar to GOC (Fig. 1).

### Fluorescence In Situ Hybridization

Fluorescence in situ hybridization (FISH) was performed on formalin fixed paraffin embedded tissue sections using the commercially available *MAML2* dual color break apart probe (Z-2014-200, Zytovision, Germany). Prior to hybridization the slides were deparaffinized utilizing a VP 2000 processor (Abbott Molecular, Des Plains, IL) with pretreatment with protease I. Following deparaffinization the slides and the *MAML2* probe were co-denatured at 80 °C for 7 min and allowed to hybridize for 22 h at 37 °C in a humidified atmosphere. The slides were then washed with agitation in 2× SSC/0.3 % NP-40 for 2 min at 72 °C and for 2 min at room temperature. Traces of detergent were removed by washing the slides in 2× SSC at room temperature. The slides were then counterstained with DAPI and a cover slip was applied using Vectashield mounting medium (H-1000, Vector Laboratories, Inc.).

A fluorescence microscope was used to evaluate the probe pattern for each case. Cells with two fusion signals of one orange and one green fluorochrome were scored as normal. Cells with rearrangements for *MAML2* gene had one normal fusion signal and one orange and one green signal at a distance from each other. A parotid gland MEC known to harbor the *MAML2* rearrangement served as a

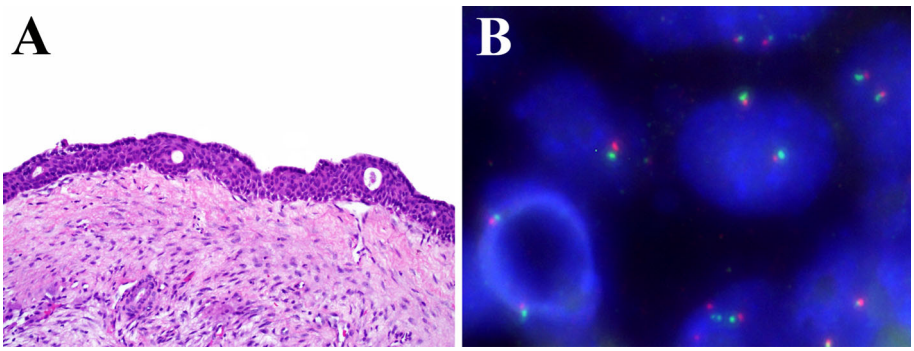


**Fig. 2** Despite their histologic similarity to cystic mucoepidermoid carcinoma, all cases of glandular odontogenic cyst (**a**) were negative for the *MAML2* rearrangement by break apart FISH (**b**)

positive control, while benign dental follicular tissue served as a negative control.

## Results

*MAML2* rearrangement was identified in all five cases of central MEC (Fig. 1). In contrast, all 21 GOCs were negative for the *MAML2* rearrangement (100 vs. 0 %; $p < 0.0001$, Fisher's Exact) (Fig. 2). In the 4 MECs where an attenuated cystic area that resembled GOC was present, the rearrangement was detected in both the solid and the cystic zones (Fig. 1).

## Discussion

While MEC is the most common malignancy of salivary glands, it may also rarely occur as a primary neoplasm of the jaws (i.e., central MEC). The definitive explanation for the presence of a salivary gland tumor within gnathic bones has been elusive. One theory is that central MECs arise from ectopically displaced benign salivary tissue [1, 4, 5]. A second theory is that central MECs arise from pre-existing benign odontogenic cysts [1, 2, 4, 21]. In light of significant morphologic overlap, GOC in particular has been identified as a likely progenitor for central MEC [2, 18]. Like low grade MECs, GOCs are cystic with an epithelial lining comprised of mixed cell types including mucinous cells and non-keratinizing squamous cells. *MAML2* rearrangements occur in up to 75 % of MEC, but their detection is not site-specific. *MAML2* rearrangements are found not just in MECs derived from the major salivary glands [23, 24, 31], but have been reported in MEC of the lung [32], uterine cervix [33], and thymus [34]. Indeed, 2 of 3 tested central MECs of the gnathic bones have been found to harbor *MAML2* rearrangements [29, 30]. GOCs have not been previously analyzed for the chromosomal translocation, but determination of *MAML2* status could help clarify their putative relationship to central MECs as a precursor lesion.

In this study, a *MAML2* rearrangement was detected in all 5 of the central MECs, but in none of the 21 GOCs. Moreover, in the central MECs the *MAML2* rearrangement was uniformly distributed throughout the solid, invasive and lining components. The lining component morphologically resembles a GOC and, based on this resemblance, GOC has been incriminated by some as a precursor from which central MECs arise [2, 18, 19]. The striking disparity in *MAML2* status suggests that GOC and central MEC are separate entities, and that GOC should not be regarded as an early or low grade form of MEC, or even as a precursor of MEC. Admittedly, some genetic alterations occur at later stages of tumorigenesis and may not be routinely encountered in early lesions, but this is not the case for *MAML2* in the development of MECs. *MAML2* rearrangements are driver alterations that are necessary for initiating and maintaining MEC tumorigenesis [35]. Indeed, they are consistently detected in the lowest grades of MEC where they represent the first and only detectable metaphase genetic alteration [28].

In addition to providing biologic insight into the relationship between GOC and central MEC, our findings also have a practical diagnostic application. In those cases where diagnosis of a cystic MEC or GOC cannot be easily made on morphologic grounds alone, the detection of a *MAML2* rearrangement would provide compelling evidence to support MEC. Potentially, a similar approach could be used for other tumors that might enter the differential diagnosis of central MEC (e.g., clear cell odontogenic carcinoma) provided that the specificity of *MAML2* rearrangements for MEC is confirmed across other types of odontogenic tumors just as we have confirmed *MAML2* status for GOCs.

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