doi: http://dx.doi.org/10.11606/issn.1679-9836.v100i1p41-48 Rev Med (São Paulo). 2021 Jan-Feb;100(1):41-8.

Review Article

Origins of central mucoepidermoid carcinoma: systematic review

Origens do carcinoma mucoepidermoide central: revisão sistemática

Khalil Abdo Kansou[1], Mozarth Matheus Silvino do Nascimento[2], Elaine Rossi Ribeiro [3]

Kansou KA, Nascimento MMS, Ribeiro ER. Origins of central mucoepidermoid carcinoma: systematic review */ Origens do carcinoma mucoepidermoide central: revisão sistemática.* Rev Med (São Paulo). 2021 Jan-Feb;100(1):41-8.

ABSTRACT: Mucoepidermoid carcinoma is a malignant tumor usually associated with salivary glands. Only 2-4% of all mucoepidermoid carcinomas have a primary intraosseous site (central mucoepidermoid carcinoma), which the etiogenesis remaining obscure, justifying the importance of researching the subject. Objective: Discover the most probable etiology (or etiologies) of intraosseous mucoepidermoid carcinoma. Method: systematic review according to the recommendations of PRISMA (Preferred Reporting items for Systematics Review and Meta-analysis Statement). The search bases consulted were: PubMed, Portal CAPES and Google academic, and after the inclusion and exclusion criteria, seven articles were selected to answer the research objective, for which the Newcastle-Ottawa tool was applied for risk analysis of bias and methodological quality. The search, selection, extraction and risk of bias were carried out by three independent researchers. Results: There are two main etiological hypotheses of intraosseous mucoepidermoid carcinoma: (1) derived from an odontogenic cyst and (2) derived from ectopic remains. Conclusions: As the evidence indicates, the pluripotent potential of cells contained in odontogenic cysts would be responsible for metaplasia and subsequent carcinogenesis. In cases derived from ectopic remains, the association with t (11; 19) translocation and the CTRC1-MAML2 fusion transcript as an etiological or early event is clear.

Keywords: Carcinoma; Etiology; Salivary glands; Submandibular gland.

RESUMO: O carcinoma mucoepidermoide é um tumor maligno geralmente associado a glândulas salivares. Apenas de 2-4% de todos os carcinomas mucoepidermoides apresentam sítio primário intraósseo (carcinoma mucoepidermoide central), cuja etiogenia permanece obscura, justificando a importância de se pesquisar o assunto. **Objetivo:** Conhecer a(s) etiologia(s) mais provável(is) do carcinoma mucoepidermoide intraósseo. **Método**: revisão sistemática de acordo com as recomendações do PRISMA (Preferred Reporting itens for Systemstic Review and Meta-analysis Statement). As bases de dados consultadas foram: PubMed, Portal CAPES e Google acadêmico, e após aplicação dos critérios de inclusão e exclusão foram selecionados sete artigos que atenderam o objetivo da pesquisa, para os quais aplicaram-se a ferramenta Newcastle-Ottawa para análise de risco de viés e qualidade metodológica. A busca, seleção, extração e risco de viés foram feitas por três pesquisadores independentes **Resultados:** São duas as principais hipóteses etiológicas do carcinoma mucoepidermoide intraósseo: (1) derivado de um cisto odontogênico e (2) derivado de restos ectópicos. **Conclusões:** Ao que as evidências indicam o potencial pluripotente de células contidas nos cistos odontogênicos seria o responsável pela metaplasia e posterior carcinogênese. Nos casos derivados de restos ectópicos é clara a associação com a translocação t(11;19) e o transcrito de fusão CTRC1-MAML2 como um evento precoce ou etiológico**.**

Palavras-chave: Carcinoma; Etiologia; Glândulas salivares; Glândula submandibular.

1. Faculdades Pequeno Príncipe, Acadêmicos Curso de Medicina. ORCID: Kansou KA - https://orcid.org/ 0000-0002-4847-0437; Nascimento MMS - https://orcid.org/ 0000-0002-2654-7456. E-mail: khalilabdo8@gmail.com, mozarthnascimento@gmail.com.
2. Faculdades Pequeno Príncipe, Pesquisadora docente Programa Ensino nas Ciências da Saúde e Curso de Medicina. ORCID: https://orcid.org/ 0000-0003-3492-217X. E-mail: elaine.rossi@hotmail.com.

Endereço para correspondência: Elaine Rossi Ribeiro. Rua Carneiro Lobo, 333. Curitiba, PR.

INTRODUCTION

Mucoepidermoid carcinoma is a malignant tumor usually associated with the salivary glands. It corresponds to 5%-10% of all tumors, affecting mainly the parotids (89.6%), the submandibular (8.4%), and the sublingual (0.4%) glands[1]. Its appearance with a primary bone site is much rarer, representing only 2%-4% of all mucoepidermoid carcinomas[2].

Its intraosseous origin, although widely discussed, is not well understood. Four possible theories for its origin are suggested: 1) entrapment of the retromolar glands in the mandible, with subsequent neoplastic transformation; 2) embryonic remnants of the development of the submandibular gland entrapped in the mandible; 3) neoplastic transformation of mucosecretory cells commonly found in the pluripotential epithelial lining of dentigerous cysts associated with impacted third molars; and 4) neoplastic transformation and invasion of the maxillary sinus lining[3].

The first case of an intraosseous (central) mucoepidermoid carcinoma was described by Lepp, in 1939, in the jaw of a 66-year-old patient[3]. Until 2003, less than 200 cases had been described so far, proving that such a finding is really rare[4].

In a paper published in January 2018, 36 publications containing reports of 147 central mucoepidermoid carcinomas were analyzed, reaching the following results: it affects slightly more women than men (51.7 and 48.3% respectively), mainly the mandible (63.3%) rather than the jaw (36.7%); it has a predilection for people aged ≥ 40 years (65.3%), and the treatment of choice was radical surgery alone (42.9%)[5].

Mucoepidermoid carcinoma affects 2.8%–15% of salivary cancers, therefore being the most common type at this site[6]. However, this neoplasm in a primary intraosseous site is much rarer, corresponding to 2%-4.3% of cases[7]. In addition, there is evidence of a predilection for the mandible (especially the posterior part) rather than the maxilla[8]. It mainly affects the age group of 40–50 years and twice as much women[9,10].

Authors state that currently there are only hypotheses requiring confirmation, such as entrapment of the salivary glands within the mandible; embryonic remnants of the submandibular gland within the mandible; neoplastic transformation of mucus-secreting cells of dentigerous cysts, and neoplastic alteration and subsequent invasion of the epithelial lining of the maxillary sinus[8,11].

Of these four hypotheses, the most prevalent (approximately 50% of the cases studied) is neoplastic transformation of mucus-secreting cells of dentigerous cysts[11]. The dentigerous cyst, by definition, is formed from odontogenic cells present in the crown of an unerupted tooth. It has, in its internal constitution, a cystic fluid and, in its external part, loose connective tissue associated with flat or cubic non-keratinized epithelial cells, making up three layers[12].

Another odontogenic cyst, although much less prevalent, is the glandular odontogenic cyst (GOC). This cyst has histological and radiological characteristics that are very similar to the intraosseous mucoepidermoid carcinoma, leading some authors to believe in a possible relationship between them[13].

However, some authors are opposed to this theory, claiming that the transition from a glandular odontogenic cyst to an intraosseous mucoepidermoid carcinoma is impossible[14].

In tomographic images, it is similar to the odontogenic cyst and the glandular odontoid cyst, presenting a uni- or multilocular radiolucency, which makes the differentiation difficult with this type of image[15].

At biopsy, keratinized stratified squamous epithelial lining can be found in the cystic lesion and, mainly, foci of mucous, epidermoid, and intermediate cells in fibrous stroma, which are characteristic of this neoplasm[9].

Brookstone and Huvos Staging is used to stage and define treatment and prognosis: "stage 1: intact cortical plate + no evidence of bone expansion; stage 2: intact cortical bone + evidence of bone expansion; stage 3: cortical perforation, rupture of the underlying periosteum or nodal growth[16]".

The treatment is divided into conservative (curettage, enucleation, marsupialization, local excision) or radical (segmental resection with or without adjacent therapy) methods, with the latter showing the best prognoses[17].

This neoplasm is generally classified as low grade and has a favorable prognosis; however, if it is on a maxillary site, the prognosis is a little more guarded[18].

Due to the difficulty in obtaining specific literature, the following research question was defined: What is (are) the most likely etiology (ies) of intraosseous mucoepidermoid carcinoma - IMEC? To seek the answer, the following objective was determined: To know the most probable etiology (ies) of intraosseous mucoepidermoid carcinoma.

METHOD

The method of choice for conducting this work was a systematic review, according to the recommendations of PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis Statement)[19].

This review was registered on the PROSPERO platform on August 3, 2019, with the identification number CRD42020145754.

The development of the guiding question used the acronym PVO[20] (an adaptation of PICO), with P standing for participants: Mucoepidermoid carcinoma with primary

intraosseous site; V, variables: Possible origins of IMEC; and O, outcomes or results: origins of IMEC.

The articles were selected from the following databases: PUBMED, CAPES Portal de Periódicos, and Google Scholar. The descriptors used, right after searching MeSH, were: ((“intraosseous mucoepidermoid carcinoma” OR “central mucoepidermoid carcinoma”) AND (precursor OR origin OR development OR etiology OR pathogenesis)) NOT report, as shown in Table 1, from May 1 to 15, 2019.

The inclusion criteria established were: being published in the last decade (except in PubMed, which was in the last 15 years); being written in Portuguese, English or Spanish; providing the full article for free; being available in full. The exclusion criteria were: editorials; opinion texts; journal columns; experience reports; works that have not been approved by the Research Ethics Committee, considering the rule for obtaining articles with high scientific evidence.

Table 1: Article search strategies

Database	Descriptors	Filters	Nº
PubMed	((“intraosseous mucoepidermoid carcinoma” OR “central mucoepidermoid carcinoma”) AND (precursor OR origin OR development OR etiology OR pathogenesis)) NOT report	# 1 Last 15 years # 2 Article in Portuguese, English and Spanish # 3 Free full article	7
CAPES Portal de Periódicos	((“intraosseous mucoepidermoid carcinoma” OR “central mucoepidermoid carcinoma”) AND (precursor OR origin OR development OR etiology OR pathogenesis))	# 1 Last 10 years # 2 Article in Portuguese, English and Spanish # 3 Free full article # 4 Be available for reading	8
Google Scholar	((“intraosseous mucoepidermoid carcinoma” OR “central mucoepidermoid carcinoma”) AND (precursor OR origin OR development OR etiology OR pathogenesis)) NOT report	# 1 Last 10 years # 2 Article in Portuguese, English and Spanish # 3 Free full article	51

Source: Authors, 2019.

This search resulted in 66 articles, from the three databases together. Then, a review was carried out by three independent researchers, initially for the exclusion of repeated articles. Next, an analysis of the title and abstract was performed. At this stage, some more exclusions were made, considering that a large number of articles that did not meet the inclusion criteria (n = 44) was found. Finally, all articles were analyzed in full by independent evaluators, to achieve the objective of this study (Figure 1).

In order to highlight the quality of the articles selected, three independent researchers used the tool Newcastle-Ottawa Scale[21] to analyze the methodological quality of the articles. This tool establishes three main domains for the analysis of the studies: Selection, Comparability, and Outcome, totaling nine points, allowing the demonstration of strong evidence in four articles, moderate evidence in three of them, which is explained in Table 2.

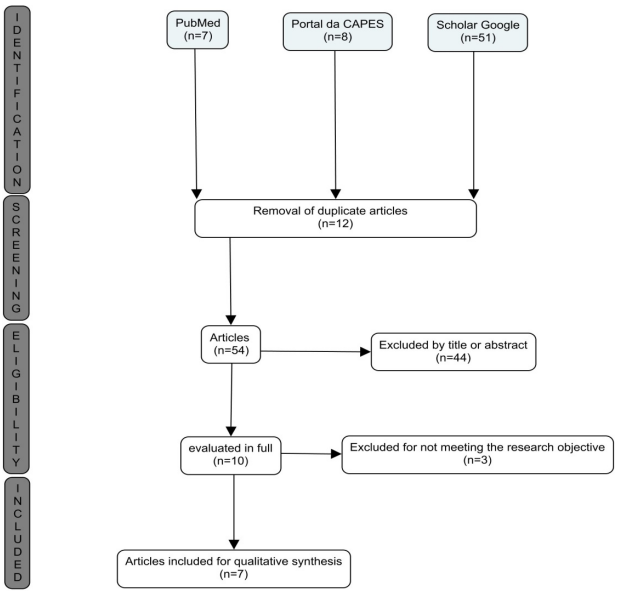

Figure 1: Flowchart of article selection

Table 2: Analysis of risk of bias according to Newcastle–Ottawa scale

ID	Design	Selection	Comparability	Outcome	Total
1	Experimental with 11 cases	3	2	3	8
2	Analysis of 25 records of patients with intraosseous mucoepidermoid carcinoma treated between 1998 and 2013.	2	1	2	5
3	Experimental with 10 cases	1	2	2	5
4	Experimental with 21 cases	2	2	3	7
5	Comparative experimental with 39 cases.	2	3	3	8
6	Experimental with three cases including one case with history of primary retromolar MEC.	1	1	2	4
7	Experimental with 85 cases.	2	3	3	8

Strong evidence - 6/9; moderate evidence - 4-5 / 9; Limited evidence - <4.
Source: author, 2019.

The extracted data were placed in a specific spreadsheet, highlighting author, title, journal, year and country of publication, objectives, methods, participants, and results. The characteristics selected for the analysis were: the methodology used in the studies (e.g., fluorescence in situ hybridization, real-time polymerase chain reaction, staining with hematoxylin eosin, or pathological analysis); the number of samples obtained for each study (must be at least three); the age and sex of each patient in the samples; verification of diagnostic accuracy, and the number of patients who relapsed.

PRESENTATION OF RESULTS

Following the application of the inclusion and exclusion criteria, seven articles that met the research objective were selected. The list of articles with general data is shown below, in Table 3, for better visualization.

Table 3: List of articles with general data

ID	Title	Authors	Journal	Year	Country	Result
1	Assessment of biologically aggressive, recurrent glandular odontogenic cysts for mastermind-like 2 (MAML2) rearrangements: histopathologic and fluorescent in situ hybridization (FISH) findings in 11 cases	Greer RO, et al.[14]	J Oral Pathol Med	2017	USA	One COG case out of 11 demonstrated MAML2 rearrangements by FISH.
2	Primary intraosseous mucoepidermoid carcinoma of the jaw: reappraisal of the MD Anderson Cancer Center experience	Bell D, et al.[22]	Wiley Online Library	2015	USA	The CRTC1-MAML2 fusion transcript was manifested in 9 of 18 cases of IMEC (intraosseous mucoepidermoid carcinoma)
3	Fluorescence in-situ hybridization identifies Mastermind-like 2 (MAML2) rearrangement in odontogenic cysts with mucous prosoplasia: a pilot study	Argyris PP, et al.[23]	Histopathology	2014	USA	All three IMECs demonstrated MAML2 rearrangement.
4	Glandular Odontogenic Cysts (GOCs) Lack MAML2 rearrangements: a finding to discredit the putative nature of GOC as a precursor to central mucoepidermoid carcinoma	Bishop JA, et al.[24]	Springer Science e Business Media New York	2014	USA	The MAML2 rearrangement was identified in all 5 of the IMEC group, but in none of the 21 GOC.
5	Central mucoepidermoid carcinoma: a clinicopathologic and immunohistochemical study of 39 Chinese patients	Zhou CX, et al.[18]	Am J Surg Pathol	2012	China	Of the 11 cases with GOC, 8 had typical IMEC histology
6	CRTC1/MAML2 fusion transcript in central mucoepidermoid carcinoma of mandible—diagnostic and histogenetic implications	Bell D, et al[25]	Ann Diagn Pathol	2010	USA	For the first time the t (11; 19) fusion transcript was identified in an IMEC
7	Cytokeratin expression in central mucoepidermoid carcinoma and glandular odontogenic cyst	Pires FR, et al.[4]	Oral Oncol	2004	Brazil	Comparing the CK expression (cytokeratins) of GOC and IMEC, there is a disparity in CKs 18 and 19.

Source: Authors, 2019.

Of the articles found, the first one was published in 2004, the next ones only in 2010 and 2012. Two articles were published in 2014, one in 2015, and the last one in 2017. As for demographic distribution, the United States were the ones that published the most, with 71.4%, while China and Brazil were similar with 14.3%, according to data in Table 2. Six articles used the experimental methodology with different numbers of cases and only one article analyzed the records, according to Table 3.

The fact that intraosseous, or central, mucoepidermoid carcinoma (IMEC) is a carcinoma with glandular characteristics, prevalent in salivary glands, and presents, even if rarely, a primary site in a bone region, raises several doubts regarding its etiology. Such doubts, if clarified, could affect its diagnosis, prognosis, and treatment[22].

Trying to find such answers, the researchers of the selected articles[4,14,18,22-25] used at least one of three distinct methodologies, in addition to the standard anatomical, pathological, and histological analysis with hematoxylin and eosin, to identify similar characteristics among possible precursors and agents involved in carcinogenesis, namely: immunohistochemistry, fluorescent in situ hybridization (FISH), and reverse transcriptase polymerase chain reaction (RT-PCR).

As it was shown, the selected articles relate to each other, sometimes agreeing, sometimes bringing up contrary facts that may cast doubt on the theories they support about the etiology of IMEC. Thus, organizing them in chronological order, as we will do, facilitates the perception of these interactions.

In 2004, Pires et al.[4], in a study whose objective was to evaluate the cytokeratin (CK) profile of central IMEC and glandular odontogenic cysts (GOC) to compare the results with the expression of CK in MEC of salivary glands, odontogenic cysts and tumors, used immunohistochemistry to identify CKs found in 23 cases of MECs - parotid (10 cases), palate (5 cases), submandibular (4 cases), retromolar (4 cases) - and in 46 odontogenic lesions - 10 dentigerous cysts, 14 keratocysts, 10 periapical cysts, and 12 ameloblastomas - in order to outline the profile of CKs of these lesions, and to establish correlations among them and among the 6 IMECs and 10 glandular odontogenic cysts (GOC).

The authors say that CKs are a group of intermediate filaments expressed mainly by epithelial cells, which include a wide range of proteins, varying in molecular weight, acidic/basic composition, and affinity[4]. The immunohistochemical expression of CKs has been considered a useful tool in the identification of different types and epithelial origins. Some studies claim that it is possible to establish the origin of a cyst or tumor through immunohistochemical expression of CKs. However, this is not easily applicable to odontogenic and glandular lesions, as the expression of CK varies according to different stages of differentiation, from embryonic to adult and specialized tissues. GOCs were used in the study because they possibly have some relationship with MECs, being a precursor or even an initial version of the tumor with less dysplasia, as later concluded by Greer et al.[4,14].

It was then shown that the excretory ducts of the salivary gland can show a broad profile of CK expression, including CKs 4, 5, 6, 7, 8, 13, 14, 16, 18, 19, and MECs show a similar profile[4]. All GOCs expressed CKs 5, 7, 8, 13, 14, 19. All odontogenic cysts expressed CKs 5, 13, 14 and 91% also expressed CK19. Only 7% of odontogenic lesions expressed CK18, which was expressed by all MECs and IMECs. In addition, almost 100% of consistency was found in the expression of CKs 7, 8, 18 in salivary IMECs and MECs, suggesting that IMEC, which presumably arises from the odontogenic epithelium, have reached the biological nature of salivary MECs. The study also suggests that MEC and GOC are distinct entities with different CK profiles and that the expression of CKs 18,19 can be useful auxiliary tools in the differentiation of these two entities[4].

Using RT-PCR, Bell et al.[25] were the first to identify the CRTC1/MAML2 fusion transcript of the translocation of the t (11; 19) genes in IMECs[25]. When the study was conducted, with the aim of analyzing the influence of the CRTC1-MAML2 fusion transcript on the prognosis, malignancy, and appearance of IMEC, it was known that this chimeric gene could be found in most MECs and would play an important role in carcinogenesis, including MECs in different locations (bronchiolar, cervix, breast), some Warthin's tumors, and clear cell hydroadenoma of the skin, but not in other types of malignancies. Collectively, these results indicate a role for the fusion gene as an early or etiological event in the development and/or malignant transformation of numerous benign and malignant epithelial tumors; however, it has not yet been found in IMECs[25].

These researchers used RT-PCR looking for the fusion transcript in three IMECs. In one of the chosen cases, case three, the patient had, in addition to the IMEC, a retromolar MEC, also investigated for the presence of the chimeric gene. The research was positive in two of the three IMEC, including in case three, and negative in one IMEC and in the MEC. In this case, both the presence and absence of the fusion transcript were critical, as they led the researchers to the following conclusions: IMECs can display the fusion transcript; in case three, both MEC and IMEC were primary tumors due to the expression of different genes; the presence of the t (11; 19) fusion gene in a subgroup of IMECs, even if speculatively, reinforces the idea of tumor development from ectopic salivary tissue, and the absence of the t (11; 19) fusion gene in a subgroup of IMECs raises the possibility of a different histogenesis of the positive transcribed group, stemming from a glandular odontogenic precursor[25].

Immunohistochemistry was used to analyze 39 IMECs, in addition to six cases of MECs originating from

salivary glands, and eight cases of GOCs for comparative studies, aiming to clarify the pathological clinical profile and the pathogenesis of IMEC[18]. Clinicopathological findings and follow-up data from 39 cases were collected and analyzed. There were 16 male and 23 female patients (median age 43 years). Sixteen cases affected the maxilla and 23 occurred in the mandible. All central MECs expressed CKs 7, 8 and 18, while only 12.5% of GOCs stained positively for CK 7, 8 and 18, in agreement with the conclusion of the study by Pires et al. 2004, stating that they are different lesions and that these markers can be useful adjuvants in differentiating IMEC and GOC[18].

In cases where there is direct evidence of an association with a preexisting odontogenic cyst, the hypothesis that mucous metaplasia and neoplastic transformation of odontogenic cyst may be the pathogenesis of IMEC is supported. The most likely pathogenesis of IMEC is the neoplastic transformation of the epithelial lining of an odontogenic cyst, the diagnosis of which shall be based on clinical, radiographic, and histopathological findings[18].

In 2014, using FISH (a method that uses molecular resources to analyze chromosomes), 23 authors tried to identify the chimeric gene MECT1-MAML2 in ten odontogenic cysts (ODCs) with prosoplasia for mucous cells and in three IMECs. All three IMECs demonstrated MAML2 rearrangement in 26%-61% of tumor cells. The successful hybridization process was observed in nine of the 10 ODCs. In two of these nine, there was MAML2 rearrangement in 12% and 24% of the lining epithelial cells, while three of the nine had rearrangement in 7%-8% of the cells; the remaining four cases were negative. MAML2 rearrangements were identified in five of the nine cases of ODCs coated by mucus-secreting cells[23].

Based on these findings, two hypotheses were elaborated: (1) a subset of ODCs can harbor the MAML2 rearrangement in the epithelial lining and can be transformed into IMEC without obvious phenotypic changes or (2) ODCs with MAML2 rearrangement would be better considered cystic IMECs. It is plausible that the gradual increase in genomic instability in the epithelial lining of ODCs through additional rearrangements of MAML2 or changes in several tumor suppressor genes, such as DCC, SMAD4, GALR1 and CDKN2A/B, can lead to malignant transformation and acquisition of the MEC phenotype, although these results shall be confirmed by additional large-scale studies including the investigation of other genes, such as DCC, SMAD4, GALR1 and CDKN2A/B[23].

Some researchers seeking to clarify the relationship between GOC and central MEC performed molecular analysis of MAML2 by FISH method on 5 IMECs and 21 GOCs[24]. The rearrangement of MAML2 was identified in all five cases of central MEC. Alternatively, all 21 GOCs were negative for MAML2 rearrangement (100 vs. 0%; p \ 0.0001, Fisher's exact). In addition, in IMECs, the rearrangement of MAML2 was evenly distributed among the solid, invasive, and coating components.

The coating component is morphologically similar to a GOC and, based on this similarity, GOC was incriminated by some as a precursor from which the central MECs arise. GOC does not appear to represent an early or low-grade form of IMEC, but an unrelated lesion. The high sensitivity and specificity of the MAML2 rearrangement for MECs points to its usefulness as a diagnostic adjuvant in the separation of cystic mucinous lesions of gnathic bones.

Therefore, they conclude that the impressive disparity in MAML2 status suggests that GOC and central MEC are separate entities, and that GOC should not be considered an initial or low-grade form of MEC, not even a precursor to MEC, which is in agreement with the results of Pires et al.[4], Zhou et al.[18] and Bishop et al.[24].

In 2015, researchers returned to the topic, but this time with a retrospective analysis of the records of 25 cases of IMECs where RT-PCR and FISH were used to search for the t (11; 19) fusion gene, whose fusion transcript is the chimeric CRTC1 gene -MAML2[22].

In two of these cases, the tumors were reclassified as odontogenic carcinoma and adenosquamous carcinoma, although the initial biopsy of both was indicative of mucoepidermoid carcinoma. Nine tumors contained CRTC1-MAML2 fusion transcript and seven tumors were negative for fusion transcription; the status of the remaining 7 tumors was not available. Of the 7 tumors negative for fusion, 4 were radiographically associated with cysts[22].

Such results led researchers to believe that tumors, where it is possible to identify the t (11; 19) translocation fusion gene, originate from ectopic remains of salivary glands and that its absence denotes an origin from a glandular odontogenic precursor. The study concludes by stating that primary intraosseous mucoepidermoid carcinomas are extremely rare tumors, usually of low grade and of a less aggressive nature. The clinical significance of malignant tumors resulting from odontogenic or de novo cysts should never be underestimated[22].

Finally, in 2017, FISH technique was used to analyze eleven cases of aggressive and recurrent GOCs in search of the MAML2 fusion transcript, evaluating a group of biologically aggressive recurrent GOCs (odontogenic cysts) to determine whether any case demonstrated unique histological characteristics or Mentor-like rearrangements (MAML2) common to IMEC[14].

Of the eleven cases, ten molecular studies were negative for the presence of the MAML2 fusion transcript and one case was positive[14]. This finding led the researchers to conclude that, although very rarely, it is possible for a GOC to originate an IMEC, contrary to Bishop et al.[24], Pires, et al.[4] and Zhou et al.[18]. However, new and broader studies have to be conducted.

CONCLUSION

The results of this work, supported by studies through the various methodologies presented, point to two main etiological hypotheses of intraosseous mucoepidermoid carcinoma: (1) derived from an odontogenic cyst and (2) derived from ectopic remains.

The evidence from the studies analyzed shows that the pluripotent potential of cells contained in odontogenic cysts would be responsible for metaplasia and subsequent carcinogenesis. The indications that a glandular odontogenic cyst could be a precursor find much more evidence against it; however, the discovery of a GOC with the MAML2 gene leads to the need for further investigation.

In cases derived from ectopic remains, the association with t (11; 19) translocation and the CTRC1-MAML2 fusion transcript as an early or etiological event is clear and its study, in addition to tumor differentiation, could result in new therapies.

However, due to its rarity, in absolute numbers, research on the origin of IMEC is scarce. Additional research on carcinogenesis through odontogenic cysts is required, as well as additional research on the MAML2 transcript and the relationship between GOC and IMEC.

Author´s participation: *Khalil Abdo Kansou*: Conception, search, analysis and interpretation of data, writing of the article, critical intellectual review. *Mozarth Matheus Silvino do Nascimento*: conception, search, analysis and interpretation of data, writing of the article, final review. *Elaine Rossi Ribeiro*: conception, planning, analysis or interpretation of data, critical intellectual review, responsibility for final approval for publication.

REFERENCES

1. Eversole LR. Mucoepidermoid carcinoma. Review of 815 reported cases. J Oral Surg. 1970;28:490-4.
2. Johnson B, Velez I. Central mucoepidermoid carcinoma with an atypical radiographic appearance. Oral Surg Oral Med Oral Patholo Oral Radiol Endodontol. 2008;106(4):51-e53 doi: https://doi.org/10.1016/j.tripleo.2008.04.029.
3. Shafer WG, Hine MK, Levy BM. A textbook of oral pathology. 3rd ed. Philadelphia: B. Saunders Company; 1974. p.359.
4. Pires FR, Chen S, Perez DE, Almeida OP, Kowalski LP. Cytokeratin expression in central mucoepidermoid carcinoma and glandular odontogenic cyst. Oral Oncol. 2004;40(5):545-51 doi: https://doi.org/10.1016/j.oraloncology.2003.11.007.
5. Souza LL, Pontes FSC, Pontes HAR, Neto NC, de Carvalho WRS, Guimarães DM. Central mucoepidermoid carcinoma: an up-to-date analysis of 147 cases and review of prognostic factors. J Craniomaxillofacial Surg. 2018;46(1):162-7. doi: https://doi.org/10.1016/j.jcms.2017.10.020.
6. Chiu GA, Woodwards RT, Benatar B, Hall R. Mandibular central mucoepidermoid carcinoma with distant metastasis. Int J Oral Maxillofac Surg. 2012;41(3):361-3 doi: https://doi.org/10.1016/j.ijom.2011.10.005.
7. Raut DL, Khedkar SA. Primary intraosseous mucoepidermoid carcinoma of the maxilla: a case report and review of literature. Dentomaxillofacial Radiol. 2009;38(3):163-8. doi: https://doi.org/10.1259/dmfr/66127543.
8. Simon D, Somanathan T, Ramdas K, Pandey M. Central Mucoepidermoid carcinoma of mandible - a case report and review of the literature. World J Surg Oncol. 2003;1(1):1 doi: https://doi.org/10.1186/1477-7819-1-1.
9. Kechagias N, Ntomouchtsis A, Mavrodi A, Christoforidou B, Tsekos A, Vahtsevanos K. Central mucoepidermoid carcinoma of the anterior region of the mandible: Report of an unusual case and review of the literature. Oral Maxillofacial Surg. 2015;19(3):309-13 doi: https://doi.org/10.1007/s10006-015-0483-8.
10. Chundru NSV, Prasanth T, Nandan SR, Rajesh A. Central mucoepidermoid carcinoma. J Cancer Res Therap. 2015;11(3):657. doi: https://doi.org/10.4103/0973-1482.138038.
11. Spoorthi BR, Rao RS, Rajashekaraiah PB, Patil S, Venktesaiah SS, Purushothama P. Predominantly cystic central mucoepidermoid carcinoma developing from a previously diagnosed dentigerous cyst: case report and review of the literature. Clin Practice. 2013;3(2):e19. doi: https://doi.org/10.4081/cp.2013.e19.
12. Caliento R, Mannarino FS, Vieira EH. Cisto dentígero: modalidades de tratamento. Rev Odontol UNESP. 2013;42(6):458-62. doi: https://doi.org/10.1590/S1807-25772013000600012.
13. Fowler CB, et al. Glandular odontogenic cyst: analysis of 46 cases with special emphasis on microscopic criteria for diagnosis. Head Neck Pathol. 2011;5(4):364-75. doi: https://doi.org/10.1007/s12105-011-0298-3.
14. Greer RO, Eskendri J, Freedman P, Ahmadian M, Murakami-Walter A, Varella-Garcia M. Assessment of biologically aggressive, recurrent glandular odontogenic cysts for mastermind-like 2 (MAML2) rearrangements: histopathologic and fluorescent in situ hybridization (FISH) findings in 11 cases. J Oral Pathol Med. 2018;47(2):192-7. doi: https://doi.org/10.1111/jop.12658.
15. Razavi SM, Yahyaabadi R, Khalesi S. A case of central mucoepidermoid carcinoma associated with dentigerous cyst. Dent Res J (Isfahan). 2017;14(6):423-6. doi: 10.4103/1735-3327.218564.
16. Brookstone MS, Huvos AG. Central salivary gland tumors of the maxilla and mandible: a clinicopathologic study of 11 cases with an analysis of the literature. J Oral Maxillofacial Surg. 1992;50(3):229-36. doi: https://doi.org/10.1016/0278-2391(92)90317-s.
17. Tucci R, Matizonkas-Antonio LF, de Carvalhosa AA, Castro PH, Nunes FD, Pinto DD Jr. Central mucoepidermoid carcinoma: report of a case with 11 years' evolution and peculiar macroscopical and clinical characteristics. Med

Oral Patol Oral Cir Bucal. 2009;14(6):E283-6. Available from: http://www.medicinaoral.com/pubmed/medoralv14_i6_pE283.pdf.

18. Zhou CX, Chen XM, Li TJ. Central mucoepidermoid carcinoma: a clinicopathologic and immunohistochemical study of 39 Chinese patients. Am J Surg Pathol. 2012;36(1):18-26. doi: 10.1097/PAS.0b013e31822be0df.

19. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1 doi: https://doi.org/10.1186/2046-4053-4-1.

20. Biruel E, Pinto R. Bibliotecário: um profissional a serviço da pesquisa. In: Anais do XXIV Congresso Brasileiro de Biblioteconomia, Documentação e Ciência da Informação. Maceió, Alagoas, Brasil; 2011.

21. Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Canção F, et al. Avaliação de estudos de intervenção não randomizados. Health Technol Assess. 2003;7(27):27. doi: https://doi.org/10,3310/hta7270

22. Bell D, Lewis C, El-Naggar AK, Weber RS. Primary intraosseous mucoepidermoid carcinoma of the jaw: Reappraisal of The MD Anderson Cancer Center experience. Head Neck. 2015;38(S1):E1312-E1317. doi: https://doi.org/10.1002/hed.24219.

23. Argyris PP, Wehrs RN, García JJ, Koutlas IG. Fluorescence in-situ hybridization identifies Mastermind like 2 (MAML2) rearrangement in odontogenic cysts with mucous prosoplasia: a pilot study. Histopathology. 2015;66(6):791-7. doi: https://doi.org/10.1111 / his.12526.

24. Bishop JA, Yonescu R, Batista D, Warnock GR, Westra WH. Glandular odontogenic cysts (GOCs) lack MAML2 rearrangements: a finding to discredit the putative nature of GOC as a precursor to central mucoepidermoid carcinoma. Head Neck Pathol. 2014;8(3):287-90. doi: https://doi.org/10.1007/s12105-014-0534-8.

25. Bell D, Holsinger CF, El-Naggar AK. CRTC1/MAML2 fusion transcript in central mucoepidermoid carcinoma of mandible-diagnostic and histogenetic implications. Ann Diagn Pathol. 2010;14(6):396-401 doi: https://doi.org/10.1016/j.anndiagpath.2010.05.009.

Received: 2020, April 23
Aceito: 2021, January 26