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Mucoepidermoid carcinoma of minor salivary glands: report of five cases

Carcinoma mucoepidermóide de glândulas salivares menores: relato de cinco casos

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ABSTRACT

Mucoepidermoid carcinoma (MEC) is the malignant neoplasm that most commonly affects the salivary glands, and may resemble reactional or vascular lesions in the mouth mucosa. This study aimed to present the socio- demographic and clinicopathological profile of five MEC cases of minor salivary glands. Cases diagnosed as MEC in an Oral Pathological Anatomy Service were selected over 19 years. Data collection, histopathological analysis, and tumor grading, as well as descriptive analysis of cases, were carried out. There were 3,313 diagnoses, 36 of which were salivary gland neoplasms, $\overline{x}$ 1.9 cases/year. Among salivary gland neoplasms, 12 (33.3%) were
malignant and 5 (13.9%) were MEC. Of the 5 cases, 3 were women aged 37-81 years. The hard palate was the
most common site affected, with a predominance of low-grade tumors. Health professionals must pay attention to lesions in the hard palate, to perform biopsy and histopathological analysis, as the correct diagnosis and histopathological grading are essential for referral and therapeutic decisions for MEC.
Keywords: Head and neck neoplasms. Malignant neoplasms. Mouth mucosa. Mucoepidermoid carcinoma. Salivary gland neoplasms.

RESUMO

O carcinoma mucoepidermóide (CME) é a neoplasia maligna que mais acomete glândulas salivares, podendo assemelhar-se a lesões reacionais ou vasculares da mucosa oral. Este estudo objetiva apresentar o perfil sócio- demográfico e clinicopatológico de cinco casos de CME de glândulas salivares menores. Realizou-se a coleta de dados, revisão histopatológica e análise descritiva dos casos diagnosticados em um Serviço de Anatomia Patológica Bucal, em 19 anos. Houve 3.313 diagnósticos, sendo 36 neoplasias de glândula salivar, $\overline{x}$ 1,9 casos/ano. Entre as neoplasias de glândula, 12 (33,3%) eram malignas e 5 (13,9%) eram CME. Dos 5 casos, 3 eram mulheres
e as idades variaram de 37-81 anos. O sítio mais prevalente foi o palato duro, com predominância de tumores de baixo grau. Profissionais de saúde devem atentar-se a lesões em palato duro, para proceder biópsia e análise histopatológica, pois o correto diagnóstico e gradação histopatológica são imprescindíveis para encaminhamento e decisões terapêuticas do CME.

Palavras-chave: Carcinoma mucoepidermoide. Mucosa bucal. Neoplasias das glândulas salivares. Neoplasias de cabeça e pescoço. Neoplasias malignas.

INTRODUCTION

Most salivary neoplasms occur in the parotid glands and eighty percent are considered benign. On the other hand, 80% of minor salivary gland neoplasms tend to be malignant[1]. Mucoepidermoid carcinoma (MEC) is the most common malignant tumor of the salivary glands, accounting for 4-10% of all major salivary gland tumors and 13-23% of minor salivary gland neoplasms[2]. Therefore, it is a diagnostic challenge, both for clinicians and pathologists, because they are uncommon tumors and their histopathological, clinical, and epidemiological characteristics are multiple and varied[2]. MEC etiopathogenesis is unknown; however, ionizing radiation is considered a risk factor[3].

These tumors can arise from the major salivary glands or several minor glands and differ in terms of the type of glandular cell involved (ductal, acinar, or myoepithelial), generating great morphological diversity in histopathology, which, combined with their rarity, makes them difficult to diagnose. Histopathological grading classifies tumors as low, intermediate, or high grade, indicating their biological behavior[4]. When it affects the minor salivary glands, it manifests as a painless mass, variably fixed, with a rubbery or soft consistency. As they are superficially located in most cases, intraoral tumors may appear as an increase in volume with a blue-red color, simulating a mucocele or a vascular tumor[5].

Malignant neoplasms are responsible for approximately 15% of deaths in Brazil, mainly caused by the delay in diagnosing those with vague symptoms, which are confused with benign conditions. Research shows that the search for specialized care tends to occur after the onset of symptoms when the stage of the neoplasia is already advanced[6].

Understanding salivary gland pathology has evolved through molecular studies over the last decade, leading to the identification of distinct entities, the development of improved diagnostic methods, as well as the identification of therapeutic targets for high-grade tumors[7]. Because MEC can form cystic patterns, diagnosis in imaging tests and fine needle aspiration biopsy (FNAB) can be difficult due to the absence, in these regions, of characteristic structures for diagnosis[8].

In this way, the present study is justified by contributing to the casuistry of MEC located in minor salivary glands in Brazil, so that diagnostic centers for oral pathologies are familiar with their characteristics and histopathological gradation, in addition to the importance of the contribution of these studies developed around the world to provide epidemiological data and try to understand the etiological factors of this tumor[9].

The objective of this research was to describe and characterize five cases of MEC in minor salivary glands, diagnosed in a reference service for mouth lesions in the state of Espírito Santo, Brazil, according to their sociodemographic, clinical, and histopathological characteristics, aiming to contribute to the identification of tumors and their variations, mainly because they are diagnosed by dental surgeons due to their location in the mouth mucosa.

METHODOLOGY

This was a cross-sectional study with a survey of all cases diagnosed as salivary gland neoplasms, based on the files of an Oral Pathological Anatomy Service (SAP Bucal) in the period from 2004 to 2022. After the initial survey, cases of malignant neoplasms of the salivary gland were identified. After identifying malignant neoplasms of the salivary glands, cases diagnosed as MEC were selected (**Figure 1**). From this moment on, the anatomopathological request forms, project forms, and medical records of the selected patients were retrieved and used as secondary sources for collecting data and research variables. A review of all histopathological slides available for each case was made for the histopathological grading of MEC cases. When evaluating histopathological characteristics, MEC has been classified into three degrees of malignancy, according to the latest classification by the World Health Organization[8]: low grade, intermediate grade, and high grade[8].

Sociodemographic and clinical data collected were: age, sex, race, smoking history, symptoms, time of perception of the pathology, type of biopsy, as well as specific data on the lesion, which includes location, size, shape, tumor gradation, and lymphadenopathy.

Histopathological analyses included the main characteristics of MEC, such as the type of epithelial cell (epidermoid, intermediate, mucous secretory, or clear cells), mitoses (present or absent), inflammatory infiltrate (present or absent), necrosis (present or absent), cystic spaces (present or absent), partial or focal keratinization, and type of stroma.

As this was a study on the prevalence of an unusual malignant neoplasm, with a report of five cases, a descriptive analysis of the data was carried out, using means and proportions, according to the nature of the variables, and presented in tables and figures. The study was submitted and approved by the Human Research Ethics Committee (HUCAM - 6.009.027).

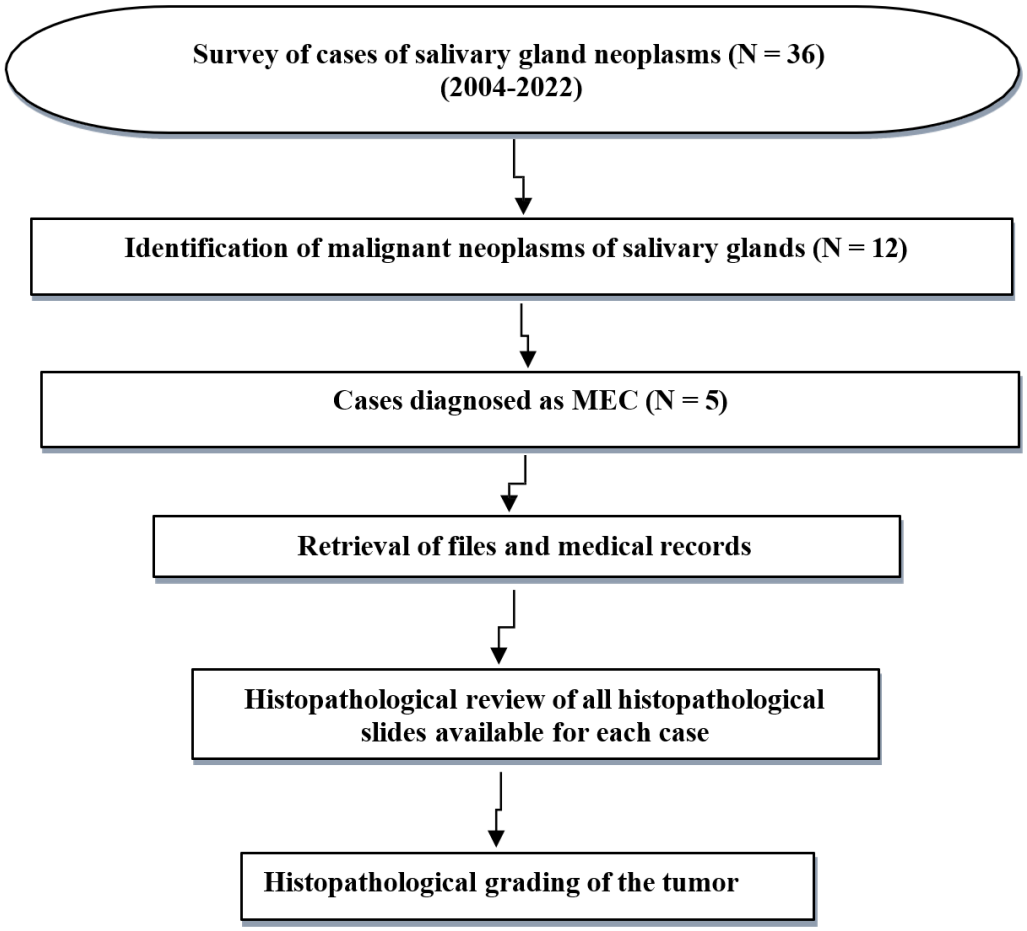

Figure 1. Flowchart for the process of surveying and collecting cases of mucoepidermoid carcinoma in the Oral Pathological Anatomy Service of the UFES Dentistry Program, from 2004 to 2022. MEC – mucoepidermoid carcinoma.
Source: Collection of the Pathological Anatomy Service – SAP – Bucal – UFES.

RESULTS

PREVALENCE

There were 3,313 diagnoses during the study period, of which only 36 were salivary gland neoplasms, $\bar{x}$ 1.9 cases per year, and a prevalence of 1.08%. Among the salivary gland neoplasms identified, 12 cases were malignant neoplasms, representing 33.3% of cases of salivary gland neoplasms. When evaluating cases of malignant neoplasms, 5 MEC cases were identified. Thus, the MEC prevalence was 0.15% for mouth lesions, 13.9% for salivary gland neoplasms, and 41.6% for malignant salivary gland neoplasms. All cases were primary malignant neoplasms of the mouth.

SOCIODEMOGRAPHIC DATA

The age of patients affected with MEC ranged from 37 to 81 years, $\bar{x}$ 51.4 ±17.3 years; therefore, from the third to the eighth decade of life, with the highest occurrence of cases in the fourth decade. People with white skin color 2 (40%) and brown 2 (40%), represented 80% of the sample, and there was 1 black patient (20%). There were 3 (60%) women and 2 (40%) men. One case (20%)

reported smoking, with a smoking history of 30 packs per year.

CLINICOPATHOLOGICAL DATA

The lesions were located on the hard palate 2 (40%), alveolar ridge 1 (20%), vestibule fundus 1 (20%), and upper lip 1 (20%). The use of a prosthesis was reported in only 1 (20%) case. The presence of lymphadenopathy was observed in 3 (60%) cases.

Clinically, the majority were described as "increased volume" or "nodule", with 1 case (20%) ulcerated, 2 cases (40%) with erythroplakia spots, 1 case (20%) bleeding, 1 case (20%) firm to palpation, and 1 case (20%) mobile to palpation (**Figure 2**). Four (80%) patients reported pain in the region.

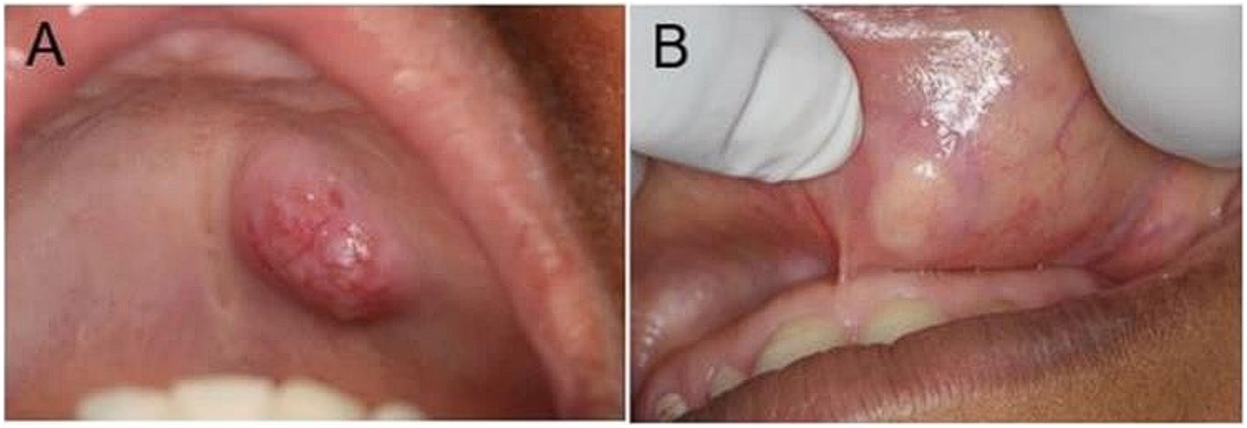

Figure 2. Clinical aspects of mucoepidermoid carcinomas. **A -** Nodular lesion with a sessile base, papular surface with erythematous, whitish areas, and telangiectasia, measuring approximately 3 cm. **B -** Nodule with a sessile base, firm in the mucosa of the upper lip, slightly pink, measuring approximately 0.8 cm.
Source: Collection of the Pathological Anatomy Service – SAP – Bucal – UFES.

The size of the lesion was recorded in 3 (60%) cases, ranging from 0.8 to 3 cm, with an average of 2.27 cm. Bone involvement was reported in one case (20%), in which the diagnosis was low-grade central MEC, presenting as a multilocular intraosseous lesion that extended from the canine to the ramus of the mandible.

The time the lesion was present, as reported by the patients (perception time), ranged from 30 days (1 month) to 3 years (37 months), with an average of 15.2 months, and in only one case, the duration of the injury was not reported by the patient (**Box 1**).

Box 1. Main sociodemographic and clinical data of mucoepidermoid carcinoma cases. (NR- Not Reported).

CASES	GENDER	AGE	LOCATION	SMOKING	PAINFUL SYMPTOMATOLOG	NEOPLASM PERCEPTION TIME	SIZE	LESION SHAPE	LYMPHADENOPAT HY	TUMOR GRADING	DIAGNOSTIC PROCEDURE
CASE 1	Masculine	44	Hard Palate	Yes	Yes	30 days	3.0 cm	Increase Volume	Yes	High Grade	Incisional Biopsy
CASE 2	Feminine	81	Vestibule Fundus	No	Yes	3 years	NR	Increase Volume	NR	Low Grade	Puncture and Biopsy
CASE 3	Masculine	52	Alveolar ridge	No	Yes	6 months	NR	Ulcerated mass	Yes	Intermediate Grade	Incisional
CASE 4	Feminine	43	Hard Palate	No	Yes	2 years	3.0 cm	Nodule	NR	Low Grade	Incisional Biopsy
CASE 5	Feminine	37	Lip	No	No	NR	0.8 cm	Nodule	Yes	Low Grade	Incisional Biopsy

When analyzing the diagnostic hypotheses set up by clinicians after first seeing patients, the following hypotheses were found: pleomorphic adenoma, basal cell adenoma, canalicular adenoma, adenocarcinoma, ameloblastoma, squamous cell carcinoma, adenoid cystic carcinoma.

After a microscopic review of the MEC cases, the histopathological grading was determined regarding the type of cells present in mucoepidermoid carcinoma of the 5 evaluated cases, 5 (100%) presented epidermoid cells, 4 (80%) presented mucoid cells, 4 (80%) showed intermediate cells, and 2 (40%) showed clear cells. No oncocytic variant was found; however, a variant with sclerosing stroma was observed (20%). (**Figure 3**).

As for the cellular arrangement, 5 (100%) of the neoplasms presented a nest arrangement of cells and 2 (40%) also presented a sheet arrangement of epidermoid cells. Regarding cystic structures, 4 (80%) of the neoplasms presented these structures, and 1 (20%) presented a more solid pattern. (**Figure 3**). There were 3 (60%) cases with cellular atypia, and 1 (20%) had mitosis. There were 4 (80%) cases with inflammatory infiltrate in their composition and 4 (80%) with areas of necrosis. No vascular, neural, or bone invasion was observed, and 1 case (20%) had cholesterol crystals in its composition. Regarding tumor grading, 3 (60%) were classified as low grade, 1 (20%) as intermediate grade, and 1 (20%) as high grade.

The biopsy performed varied, taking into account the extent of the lesion and the site of tumor involvement, whether in soft tissue, bone, or both. In only one case, the biopsy was performed for hard and soft tissues. A diagnostic puncture was performed followed by a biopsy, four incisional biopsies, and one excisional biopsy. The patients were referred for oncological treatment at reference hospitals in the region.

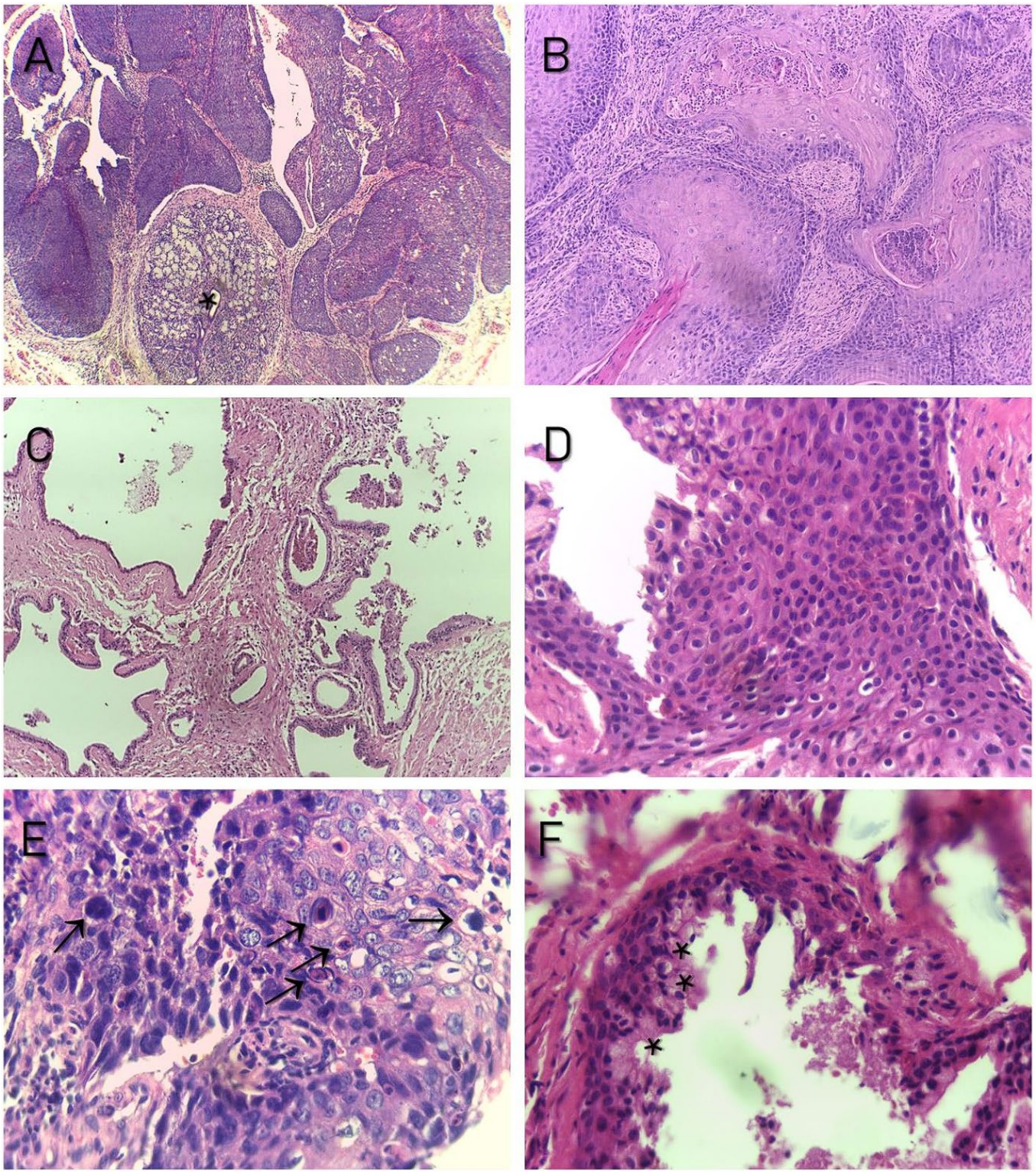

Figure 3. Histopathological characteristics observed in mucoepidermoid carcinomas. **A** – Nests of epidermoid cells and mucous acini with degeneration (asterisk) - HE, 4x objective. **B** – Nests of squamous cells and connective tissue surrounding the islands with diffuse lymphocytic inflammatory infiltrate - HE, 10x objective. **C** – Numerous cystic cavities of varying sizes - HE, 10x objective. **D** - Nest of intermediate cells - HE, 40x objective. **E** – Nest of epidermoid cells displaying intense cellular pleomorphism and numerous typical and atypical mitoses (arrows) - HE, 40x objective. **F** – Cyst with epithelial lining composed of epidermoid and mucous secretory cells (asterisks) - HE, 40x objective.

Source: Collection of the Pathological Anatomy Service – SAP – Bucal – UFES.

DISCUSSION

MEC represents 10-15% of salivary neoplasms, and although it is the most common malignant neoplasm of the salivary glands, its low incidence is a diagnostic challenge, as well as for carrying out clinical trials and developing treatment guidelines[10].

MEC has a controversial and questionable origin and may be related to ionizing radiation, smoking, and genetic factors[11]. In this study, as only one patient reported using tobacco and none of the other cases reported a history of radiation exposure, other etiological possibilities described in the literature were considered.

In addition to these factors, MEC can occur due to metaplasia of the epithelium of odontogenic cysts, entrapment of tissue from the submandibular and sublingual glands during embryonic development, and entrapment of minor salivary glands in the retromolar region. They can also arise from the epithelium of the maxillary sinus and the iatrogenic entrapment of minor salivary glands[12], giving rise to the intraosseous variant, which was observed in one case in the present sample.

The clinical presentation of MEC may vary according to its location or tumor grade. These presentations assist in the diagnostic process. When located in minor salivary glands, the color can vary from blue and reddish to purplish and may have a floating appearance[13,14]. In this study, two cases presented an increase in volume with a floating appearance, one in the hard palate and the other in the vestibule fundus, requiring the clinician to be alert to malignant lesions in these regions.

A relationship between the occurrence of pain and high-grade MEC[15,16] can also be observed. Tumors in minor salivary glands are generally painless, but there are exceptions, with cases associated with pain and paresthesia, especially when associated with high grade[17]. In this study, the high-grade case presented painful symptoms. Low-grade and intermediate-grade lesions are usually slow-growing, while high-grade MEC shows more aggressive and rapid growth, which would be decisive for the patient to seek help from a healthcare professional more quickly[18]. In this study, the time of perception depending on the patient varied from 30 days to 3 years, and the appearance of the lesion and histopathological grade may have influenced it. In this study, there was one case located in the hard palate, with the appearance of an ulcerated, painful mass, and the time of perception was 6 months. In histopathological analysis, the neoplasm was classified as high-grade. Low-grade cases were submucosal nodules or increased volume and had a perception time of 2 to 3 years. With this, we realized that a more serious clinical aspect of the injury, whether associated with pain or not, contributed to the patient's search for care.

The palate is the most common site for MEC of minor salivary glands to be affected, probably due to the large concentration of salivary glands in the region. In this study, two cases occurred in the hard palate. When they present as an increase in volume, they can be confused with infections of dental origin or benign tumors with mucinous components[15]. Cases on the palate may also resemble necrotizing sialometaplasia, cystadenoma, inverted papilloma, pleomorphic adenoma, chronic sialodenitis, odontogenic cysts, plasmacytoma, and Langerhans cell histiocytosis. In the diagnosed cases, diagnostic hypotheses of malignant pathologies were also raised by the clinicians responsible for the care, including adenosquamous carcinoma, sebaceous carcinoma, squamous cell carcinoma, clear cell tumors, acinar cell carcinomas, metastatic renal cell carcinoma, low-grade adenocarcinoma, adenoid cystic carcinoma, and lymphoma[16,19].

In this study, the only differential diagnosis mentioned that is not commented on in the literature as a possible differential diagnosis of MEC was ameloblastoma. This hypothesis was raised for intraosseous MEC and is justified. Central or intraosseous MEC is a rare variant and represents less than 5% of all mucoepidermoid carcinomas[20].

MEC can form cystic and solid patterns and tumors that are largely cystic can present diagnostic problems in imaging tests and fine needle aspiration (FNA) if the puncture is performed in cystic areas[21]. In this study, 4 cases presented cystic structures in their constitution and only one presented a more solid pattern. Although (FNA) is a simple, low-cost technique that provides a quick diagnosis and offers a lot of information, its usefulness is limited by its low sensitivity and high rate of false negatives[21]. As the

clinical appearance is not sufficient for diagnosis, it is essential to perform a biopsy for analysis and definitive diagnosis.[21] Imaging exams such as computed tomography and magnetic resonance imaging are used to evaluate the size, extension, and depth of tumors for preoperative procedures; however, magnetic resonance is widely accepted as a superior technique for evaluating soft tissue pathologies[22].

Tumor grading has proven useful in establishing therapy, with low-grade tumors undergoing surgery and high-grade tumors receiving adjuvant radiotherapy[17,23]. In this study, it was possible to reevaluate the slides and establish the tumor grading as recommended by the WHO.

CONCLUSION

MEC is a low-prevalence neoplasm; however, among malignant neoplasms of the salivary gland, it is the most common. The histopathological diagnosis of mucoepidermoid carcinoma is challenging due to the numerous possible morphological aspects of the disease, such as the sclerosing variant found. Nevertheless, histopathological diagnosis and tumor grading are important in treatment decisions.

High-grade tumors and the clinical appearance of the lesion, especially when in the presence of an ulcer, help the patient to seek help more quickly than low-grade cases, with slower growth, and an increase in volume or nodule with normochromic aspects. Clinicians should be aware of painful swelling in palates in adult women and proceed with investigation through biopsy. Biopsy is still the most used form of diagnosis in reference centers for mouth injuries.

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