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Central mucoepidermoid carcinoma of the maxilla, a challenging diagnosis

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Abstract

Objective: To present a pictorial review on central mucoepidermoid carcinoma.

Case report: Central mucoepidermoid carcinoma (CMEC), also known as intraosseous mucoepidermoid carcinoma (IMEC), is an extremely rare disease (less than 2-4% of all MEC). However, CMEC is the most frequent malignant salivary gland tumour found in intraosseous locations. Due to this unusual location, diagnosis of CMEC can be challenging. Therefore, CMEC is often mistaken for other intraosseous or odontogenic pathologies. Radiological assessment should include panoramic X-Ray, CBCT and thoracic CT, which should be performed after diagnosis. The recommended treatment includes radical resection surgery, followed by radiotherapy if indicated. A long-term follow-up is recommended for up to 10 years.

Conclusion: The authors experienced the challenging diagnosis of CMEC through the case of a patient who presented with a slowly growing palatal mass.

Keywords: mucoepidermoid carcinoma, central mucoepidermoid carcinoma, odontogenic cyst, intraosseous tumour

Introduction

Salivary gland tumours represent 3-5% of head and neck tumours. The most common primary malignant salivary gland tumour is mucoepidermoid carcinoma (MEC), followed by adenoid cystic carcinoma, and acinic cell carcinoma [1, 2]. The MEC is mostly found in major or minor salivary glands, and is the most frequent salivary gland malignancy. It accounts for about 30% of malignant salivary gland tumours and 10% (2,8-15%) of all salivary gland tumours [3, 4]. The central MEC (CMEC), also known as the intraosseous MEC (IMEC), is an extremely rare disease (less than 2-4% of all MEC) but it is the most frequent malignant salivary gland tumour found in intraosseous locations [3, 5].

The pathogenesis of CMEC is still subject to debate. It may originate from ectopic salivary glands, or result from neoplastic transformation of odontogenic cyst or from the epithelial lining of the maxillary sinus. The CMEC affects twice as many women as men. The CMEC has been described in all ages, from 1 to 78 years, with most of cases occurring during the fourth and fifth decades of life [4, 6]. The mandible is affected three times more often than the maxilla, and predominantly in the premolar/molar region [3, 6, 7]. The association with dental cysts and /or impacted teeth is described in up to 50% of cases and may support one of the aetiologic hypotheses, which is the neoplastic transformation of the epithelial lining of an odontogenic cyst [8].

Due to the intraosseous location, diagnosis of CMEC can be challenging. Therefore, CMEC is often mistaken for other intraosseous or odontogenic pathologies such as odontogenic keratocystic tumour, ameloblastoma, dentigerous cyst, or glandular odontogenic cyst (GOC) [4]. Consequently, the CMEC diagnosis is often delayed [8]. The recommended modality of treatment is the radical resection surgery. Radiotherapy may complete the treatment if indicated.

The authors experienced the challenging diagnosis of CMEC through the case of a patient who presented with a slowly growing palatal mass, with the persistence of a radiolucent lesion of the left maxilla after extraction of an impacted wisdom tooth.

Case report

A 50-year-old male patient was referred by a maxillofacial surgeon from a private practice, to our department of maxillofacial surgery in April 2020, during the Covid pandemic time, for the management of a cystic lesion in the left posterior maxilla. This lesion was slowly growing since the extraction by a general dental practitioner in another hospital of an impacted wisdom tooth with an adjacent cystic lesion (tooth n°28) two years prior the present consultation. The extraction was described as very difficult by the patient. Unfortunately, no pathological examination was requested after the surgery. The patient was unable to retrieve previous panoramic X-

rays or dental X-rays. The patient's past medical history was unremarkable, except an allergy to penicillin. The patient reported no tobacco or alcohol consumption. No pain or bleeding was associated with the growing lesion. There was no change in occlusion, no complaint of dysphagia, and no trismus. At extraoral examination, there were no signs of facial asymmetry, and no neck lymph nodes were individualized. Intraoral examination showed a palatal fluctuating mass close to the mid-palatine suture, with intact but slightly blue-appearing overlying mucosa, extending between tooth n°24 and n°27 (Figure 1). There were no obvious signs of infection.

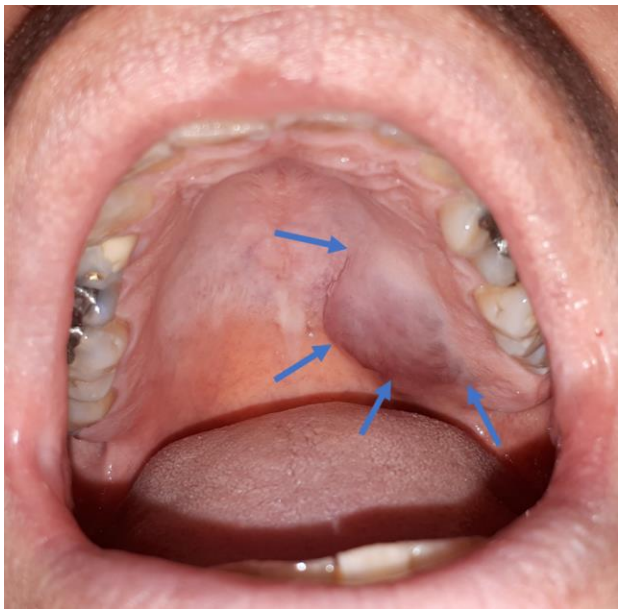

Fig. 1. Intraoral aspect of the left palatal mass. Blue arrows show the extension of the lesion.

The teeth had no abnormal mobility, and the vitality test by cold stimulus was positive, indicating the absence of pulp necrosis.
The panoramic X-ray showed a radiolucent lesion in the posterior left maxilla, with the loss of the apical part of distal root of tooth n°27 (Figure 2). This aspect was compatible with the traumatic wisdom tooth extraction (n°28) related by the patient.

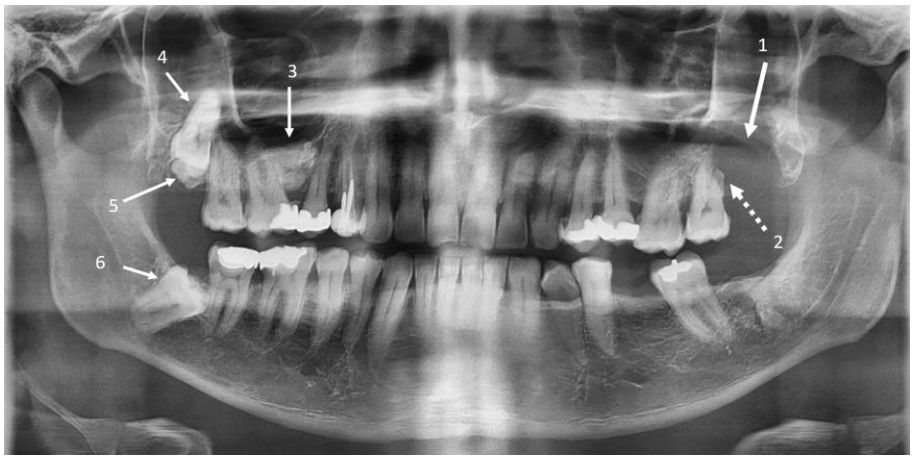

Fig. 2. Panoramic X-ray. 1. Ill-defined radiolucent lesion in the area of removal of the tooth n°28. 2. External resorption of the distal root of the tooth n°27 in relation with the radiolucent lesion. 3. Odontoma between the roots of teeth n°15 and n°16. 4. Impacted tooth n°18 surrounded by the pneumatization of the alveolar bone by the right maxillary sinus. 5. Possible supernumerary tooth close to the occlusal area of the tooth n°18. 6. Impacted tooth n°48.

Further exploration by Cone Beam Computed tomography (CBCT) (Figures 3-5) showed a multilocular radiolucency in the posterior left maxilla with bone septa in the internal aspect of the lesion (Figure 3). Expansion of the vestibular and palatine cortex were present (Figure 4). Resorption of palatal and distal roots of tooth n°27 was observed (Figure 3). Some degree of osteolysis of the buccal and palatal walls was identified (Figures 3, 4). The borders of the radiolucency were ill-defined at some locations (Figures 3-5). A discrete thickening of mucosal walls of the left maxillary sinus was seen in the vicinity of the lesion (Figures 3-5).

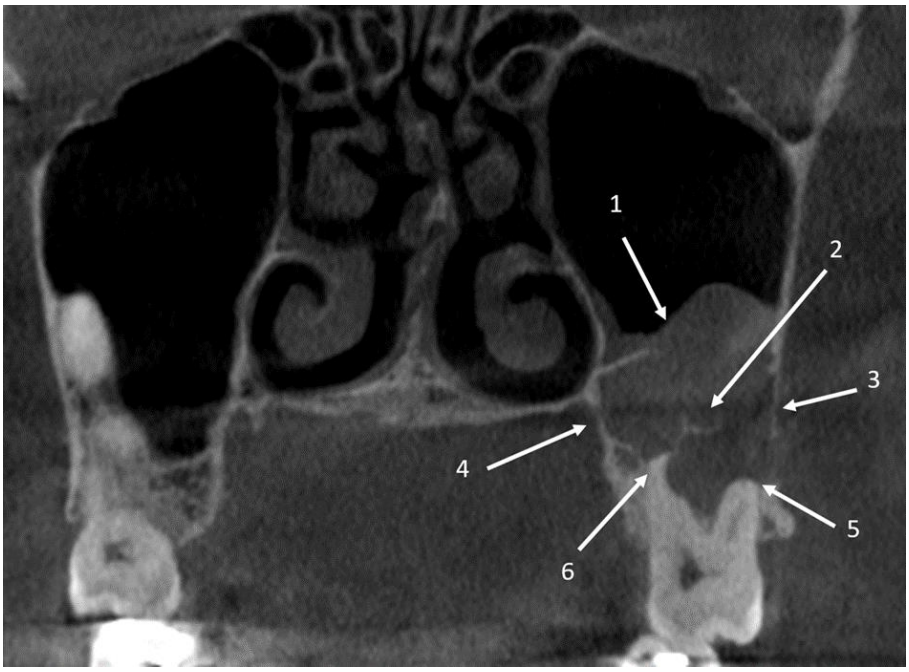

Fig. 3. Planmeca Promax 3D Mid. Coronal view at the level of the tooth n°27. 1. Extension of the lesion in the left maxillary sinus. 2. Internal septa in the lesion. 3. Thinning of the vestibular cortex. 4. Thinning of the palatine cortex. 5. External resorption of the distovestibular root of the tooth n°27. 6. External resorption of the palatine root of the tooth n°27.

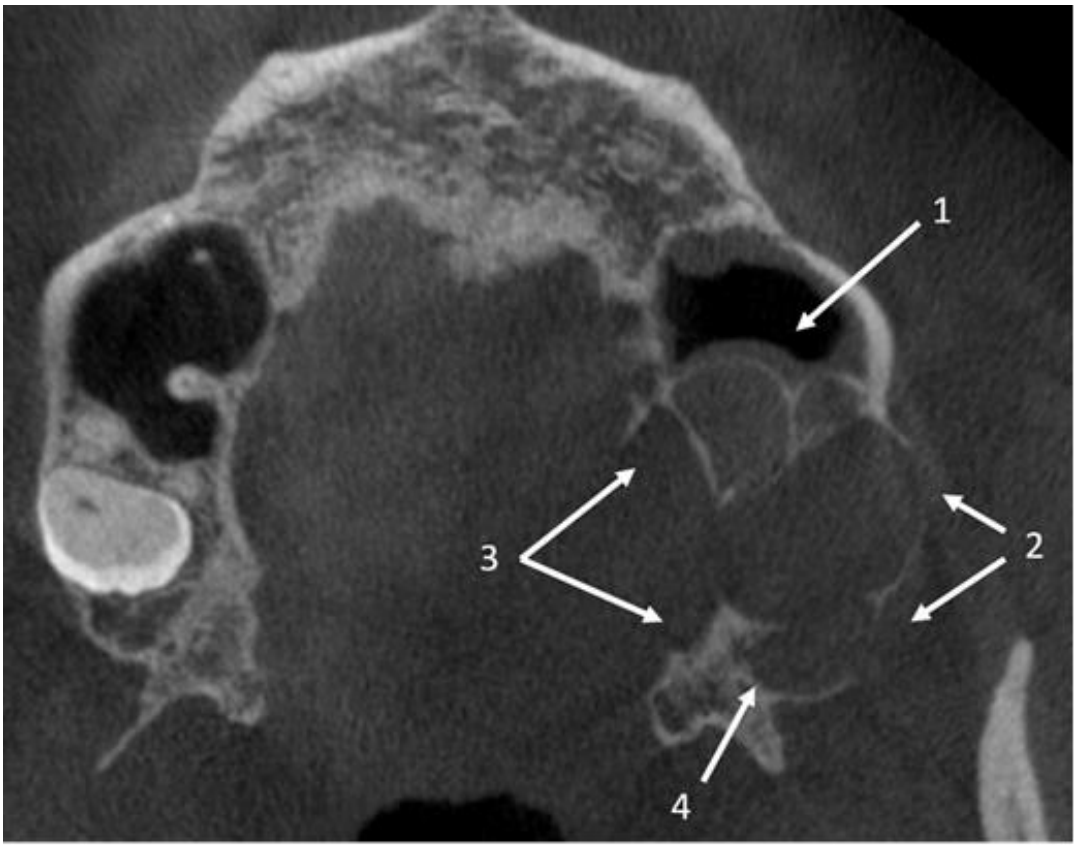

Fig. 4. Planmeca Promax 3D Mid. Axial view. "Soap bubbles" radiolucent lesion. 1. Anterior expansion in the left maxillary sinus. Presence of thickening of the mucosa of the left maxillary sinus. 2. Lateral expansion and thinning of the vestibular cortex. 3. Palatine expansion and important thinning of palatine cortex. 4. Posterior expansion and slight involvement of the left pterygoid process.

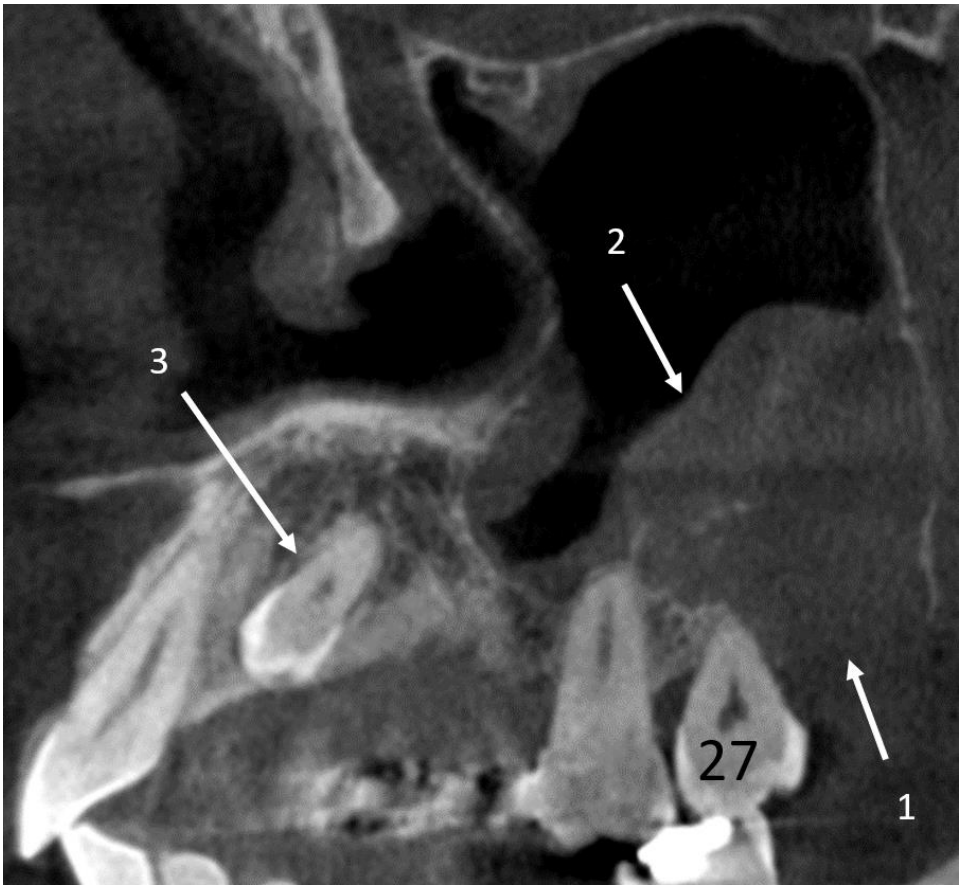

Fig. 5. Planmeca Promax 3D Mid. Sagittal view. 1. Ill-defined osteolysis of the alveolar crest distal to the tooth n°27. 2. Ill-defined cranial extension of the lesion inside the left maxillary sinus. 3. Supernumerary tooth palatine to the tooth n°23.

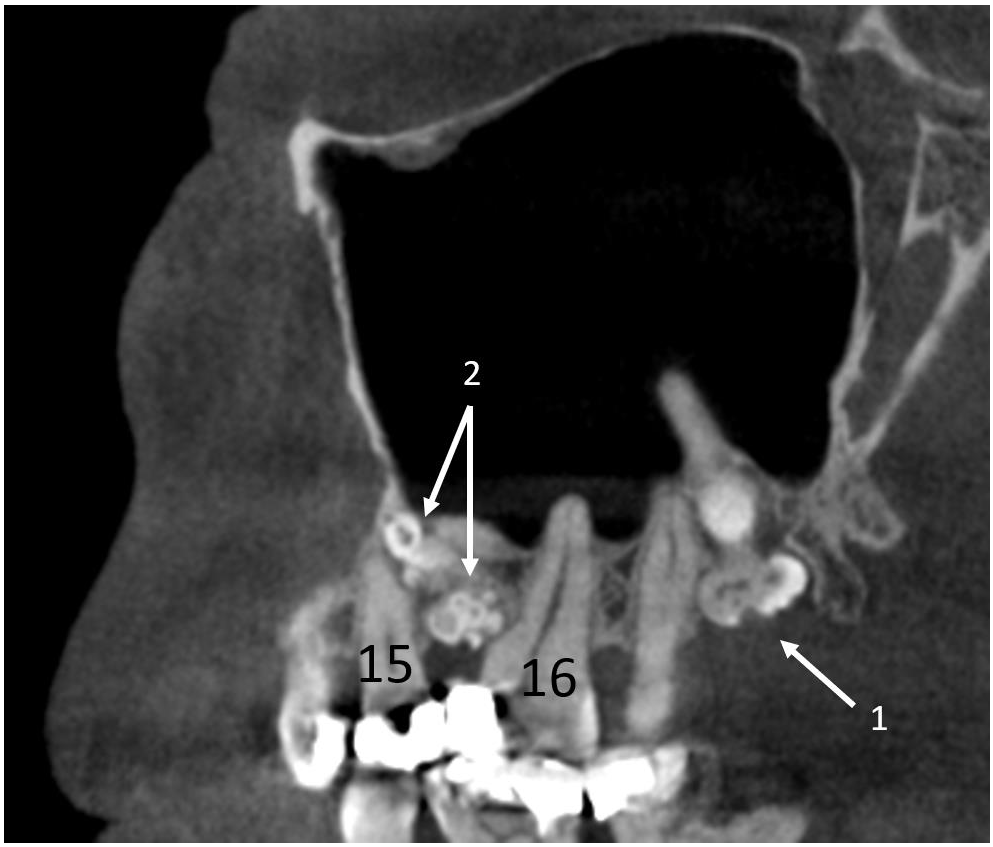

Fig. 6. Planmeca Promax 3D Mid. Sagittal view. 1. Odontoma occlusal to the impacted tooth n°18. Odontoma between roots of teeth n°16 and n°15.

Additionally, the preoperative CBCT showed that the patient also presented a left impacted supernumerary tooth in the anterior left maxilla (Figure 5) and two odontomas in the right maxilla (Figure 6).

Based on the clinical and radiological examination, preoperative diagnosis was oriented towards a residual odontogenic cyst, in relation with the extraction of the impacted wisdom tooth 28, even though osteolysis was present in some locations. Curettage-biopsy under general anaesthesia was performed in July 2020. During the surgery, the lesion was quite brittle and adherent to the underlying bone. Macroscopic pathological examination showed a partially cystic, poorly defined lesion. Microscopic findings showed glandular structures bordered by mucoid cells containing patches of mucus. Cells presented an abundant cytoplasm and a central

nucleus. Within the lesion, there were nuclei with more important cytonuclear atypia and a large nucleolus. Intermediate cells of the tumor showed p40 positivity at immunohistochemical examination. PAS and blue alcyan staining showed the presence of secretory vacuoles within the lesion. The final diagnosis was a low grade mucoepidermoid carcinoma with incomplete resection.

As the pathological examination revealed a mucoepidermoid carcinoma, a thoraco-abdominal Computed Tomography (CT) scan was realized and showed no distant lesion. Head and neck MRI showed no residual lesion and no neck lymph node. The oncological treatment was completed with an en-bloc resection by partial maxillectomy two weeks later, from tooth n°24 to the pterygoid processes (included in the resection), and to the midline of the palate. The surgical defect was rehabilitated with a palatal obturator prosthesis.

After the second resection the pathological diagnosis was that of a central mucoepi-dermoid carcinoma. The second resection had clear margins, and showed only a small residue of carcinoma of 5 mm. Molecular genetic testing of the tumour showed the presence of a translocation t(11;19) (q21;p12-13) involving MAML2 in 87 % of nuclei.

The staging was ypT1cN0M0 according to the 8th edition of TNM classification, considering that central mucoepidermoid carcinoma is classified as a primary bone tumour. Favourable prognostic factors were low grade tumour, R0 margins and cN0 status. Negative prognostic factor was perineural infiltration, only seen in one image, which was distant from the resection margins. No adjuvant therapy was necessary, and a regular clinical follow-up was proposed, with thoracic and head and neck CT scan every year.

No evidence of local recurrence or regional and distant metastasis was found 2 ½ years after surgery.

Discussion

Clinical diagnosis of CMEC remains a challenge. The symptoms are not pathognomonic and include painless swelling of the jaw, paraesthesia, toothache, trismus, and are in relation with the tumour location. CMEC is often an accidental finding on X-ray, showing a radiolucent area, with with ill-defined margins. This lesion can mimic other osteolytic and odontogenic lesions and is often associated with odontogenic cysts. The final diagnosis is made with a biopsy or after curettage.

In the study of He et al., concerning 24 patients with CMEC [4], the initial clinical diagnosis was coincident with the pathological diagnosis in only 12,5% of cases.

The pathogenesis of CMEC remains unclear. Different hypotheses are evoked such as [5]:

1. Ectopic salivary gland tissue entrapped within the mandibular bone during development, occurring mostly inferior to the mandibular canal. This can occur from

embryonic remnants of the submandibular and sublingual glands, or from retromolar mucous glands. The mucous-type secretory cell nests can undergo neoplastic transformation. A description of malignant transformation of nests of mucous-secreting cells during puberty exists, since growth factors could influence neoplastic degeneration [4, 7, 9].

2. Transformation of mucous cells usually found in odontogenic cysts (ODC). The pluripotent epithelial lining of impacted third molars can undergo malignant degeneration to mucoepidermoid carcinoma [6]. This hypothesis is supported by mucous prosoplastic phenomenon occasionally present in the epithelial lining of ODCs, and the coexistence of CMEC and odontogenic cysts in 32-48% of cases [10, 11]. Eversole et al., (12) found that 48% of mandibular CMEC are associated with dental cysts or impacted teeth, whereas Brookstone and Huvos [13] reported a rate closer to 32%. This relation was not found by He et al. [5].

3. Neoplastic transformation and invasion from the epithelial lining of the maxillary sinus

4. Neoplastic transformation of entrapped minor salivary glands within the maxilla or submucosal mucous glands with intraosseous extension [5].

However, the etiology of CMEC remains ambiguous.

To support the hypothesis of intraosseous inclusion of salivary tissue, a study by Bouquot et al., [14] demonstrated the presence of salivary tissue in 0,3% of bone specimens of all jaw bones. Thirteen of their 5034 marrow samples (0.3%) contained heterotopic acinic hamartomas, salivary choristomas, embryonic salivary rests, or entrapped surface glands.

To support the hypothesis of transformation of mucous cells of ODC, CMEC are located predominantly in the mandibular premolar/molar region, where nearly 50% of them are associated with dental cysts or impacted teeth [12].

An association with a calcifying odontogenic cyst and CMEC is also described by Isshiki-Murakami et al. [15].

In order to differentiate CMEC and glandular odontogenic cyst (GOC), immuno-histochemical cytokeratine profile has been suggested. Different CK were tested and were non-conclusive: CK 19, CK7, CK14, CK 18, CK 13 [16].

For other authors, CK7, CK8 and CK18 are systematically positively stained in CMEC, whereas they are rarely positive in GOC [4].

Pires et al., also found differences between CK expression in GOC and CMEC. CK18 was expressed in 100% of CMEC and only in 30% of GOC, and CK19 was expressed in 100% of GOC and only in 50% of CMEC [17].

To date, direct evidence of these different hypotheses has not been documented with certainty [15]. Therefore, histology and immunohistochemical markers cannot help making the difference between GOC and CMEC.

Molecular genetic testing could be helpful, involving MALM2 (Mastermind-like2) rearrangements. This has been studied in ODC) and in GOC. CMEC shows a unique genetic profile, which can help to establish the diagnosis via fluorescence in-situ

hybridisation (FISH) analysis [6]. More than 50% of CMEC demonstrate the CRTC1-MAML2 transcript which can easily be identified by FISH [7].
Rearrangements of MAML2 have been detected in about 75% of salivary glands MEC, mostly in low and intermediate grade MEC [18]. MAML2 rearrangements have been found in two thirds of CMEC.
GOC may share some histopathologic features with CMEC, which could suggest that GOC may be a precursor lesion or may be a low-grade form of CMEC [11, 18, 19]. Therefore, we should be careful in the interpretation of small incisional biopsies. The difference can be made by analysis of MAML2 gene rearrangements. GOC were once thought to be systematically negative for these gene rearrangements while CMEC were positive. This could suggest that GOC and CMEC are separate entities, but the limitation of these studies is the very small number of tested cases. This finding does not totally exclude the possibility that CMEC may develop from a pre-existing GOC [1, 16]. This hypothesis is supported by the findings of Greer et al., in 2018 [20] and other authors [10], who reported MAML2 rearrangement in lesions which presented histologic criteria for GOC.
Bishop et al., [18] have reported the lack of MAML2 rearrangements in GOC (n=521), whereas CMEC (n=55) consistently showed the MAML2 rearrangements. For these authors, this discredits the odontogenic origin of CMEC.
Argyris et al., [10] demonstrated the presence of MAML2 rearrangements in a small subset of ODC with mucous prosoplasia.
In addition, the t(11;19) and its CRTC1-MAML2 fusion gene transcript have been identified in MEC at various sites (breast, lung), and are associated with a subset of MEC [6, 10]. More than 50% of CMEC manifest the CRTC1-MAML2 fusion gene transcript [6].
The t(11;19) fusion gene transcript CRTC1-MAML2 was analysed in 18/25 patients presenting with CMEC by Bell et al., [6], with 9/18 CMEC containing the fusion transcript CRTC1-MAML2.
Their conclusion was the following:

- in the presence of t(11;19) fusion transcript-positive CMEC, the origin from ectopic salivary rests can be considered.
- in the absence of the t(11;19) fusion gene in a subset of CMEC suggests that a different histogenesis is possible, originating from a glandular odontogenic precursor.

In this case report the CMEC showed the presence of translocation t(11;19) (q21;p12-13) involving MAML2 in 87 % of nuclei.

Radiological aspects

X-ray imaging consists of panoramic radiography and CT scan or CBCT for evaluating the maxillofacial area.
Radiographically, lesions are usually well-circumscribed, unilocular or multilocular, with radiolucent areas. Radiological identification is sometimes difficult as CMEC may be confused with benign or malignant odontogenic tumours such as

ameloblastoma, GOC, and odontogenic keratocystic tumour [3, 7]. Association with impacted teeth and/or dental cyst is found in up to 50% of cases. Location of CMEC is predominantly the mandibular premolar/molar region [7].
The presence of root resorption can be associated. The aggressive behaviour is correlated with cortical bone perforation and/or extension to the surrounding soft tissues [3, 21].
In our case report, the history of difficult wisdom tooth removal with the presence of an osteolytic lesion two years before, as well as the absence of soft tissue infiltration can lead to confusion with the radiological aspect of a benign lesion such as ODC or tumour, or odontogenic infectious disease.

Classification

Brookstone and Huvos [13] have proposed a classification system based on the radiographic properties of the tumour, which can be helpful in determining the prognosis.
Stage 1: lesions with an intact cortex layer, and without bony expansions. These lesions have the best prognosis.
Stage 2*:* Lesions are surrounded by intact bone that has undergone some degree of expansion, without alteration of the integrity of the cortex.
Stage 3*:* Lesions are associated with any instances of cortical perforation, break-down of the overlying periosteum, or nodal spread, associated with the poorest prognosis.
According to this classification, the patient described in this case report was considered as stage 3.
However, the standard classification of bone tumours from the 8th edition of UICC TNM classification of malignant tumours, states that CMEC should be considered as a primary bone tumour and not a as a primary salivary gland tumour [22]. According to this TNM classification, the patient's staging was ypT1cN0M0.
Diagnostic criteria for CMEC were defined by Alexander et al. [23], and modified by Waldron et al., [24], and are the following:
(a) Presence of intact cortical plates on CT,
(b) Radiographic evidence/feature of bony destruction,
(c) Absence of a primary lesion in the salivary glands or elsewhere which can mimic the histologic features of MEC,
(d) Exclusion of an odontogenic tumour,
(e) Histopathologic confirmation,
(f) Detectable intracellular mucin production (positive PAS staining or mucicarmine staining).

Pathological examination

Li et al, [4] analysed 133 cases of CMEC in the literature. In their review, CMEC appears mostly as a low-grade tumour (59 cases of low-grade, 31 cases of

intermediate grade, 15 cases of high-grade, and 28 cases unspecified).
Merna et al., [8] included 104 histologically confirmed cases of CMEC, and showed 54% of low-grade tumours, 29% of intermediate grade, and 13% of high-grade tumours. Association with an ODC was found in 54% of cases.
De Souza et al., [25] found 147 cases of CMEC, most of which were histologically classified as a low-grade (54.4%) with a favourable prognosis. Local recurrence was observed in 16 patients (10.88%), 11 of which were of low-grade. Distant metastases were found in 3 patients (2.0%), 2 of which were of low-grade.

Differential diagnosis

The differential diagnosis of unilocular CMEC consists of: radicular cyst, paradental cyst, calcifying epithelial odontogenic cyst, benign odontogenic keratocystic tumour, and dentigerous cyst. Multilocular lesions have an internal structure resembling a honeycomb, and can be misdiagnosed with an ameloblastoma [4].
Other diagnoses which can be mentioned are ameloblastic fibroma, odontogenic myxoma, salivary gland tumours including MEC, adenoid cystic carcinoma, intraosseous squamous cell carcinoma, metastatic tumours to jaws from lung, kidney or prostate cancer [26].

Treatment

Radical surgery with 5 mm histologic margins is the best choice of treatment and is associated with a 4-13% recurrence rate contrasting with 40% with conservative treatment only (enucleation, curettage, marsupialization, marginal resection, debridement) [3, 6].
Neck dissection is recommended in cases in which the primary lesion is larger than 2 x 2 cm with high-grade type CMEC, and/or in case of cN+ status [5].
Postoperative radiotherapy is recommended for high-grade tumour, or with positive margins without possibility of a second resection, or in presence of perineural invasion [5].
Metastases have been reported in approximately 9-12% of cases, primarily in regional lymph nodes, lungs, and brain [3, 6].
The mortality rate is 10% of patients, often as a result of local tumour recurrence [3].
Concerning chemotherapy, MEC harbouring the CRTC1-MAML2 translocation may be a valid target for tyrosine kinase inhibitor therapy [6].

Follow-up

A long-term follow-up is recommended up to ten years, with thoracic, and head and neck CT scan every year.
Poor prognosis factors are male gender and high histological tumour grade [8].

In conclusion, the origin of the CMEC in this case report could not be identified with certainty. However, according to the findings of Bell et al. the presence of 87% of MAML2 translocation t(11;19) (q21;12-13) in the tumour suggests an origin from ectopic salivary tissue, rather than from a glandular odontogenic precursor [6]. Therefore, the preferred hypothesis concerning this patient is that of neoplastic transformation and invasion from the epithelial lining of the maxillary sinus, or from neoplastic transformation of entrapped minor salivary glands within the maxilla. Malignant transformation of a maxillary ODC seems less probable according to these MAML2 rearrangements, even though the lesion seemed to develop on the site of an impacted wisdom tooth.

As it is often the case in the literature, the history of the patient and radiographic findings lead the authors to misdiagnose the lesion which was initially treated as a benign ODC. Fortunately, the treatment after histopathological diagnosis was corrected with an en-bloc resection of the left maxilla with clear margins and reconstruction with an obturator prosthesis. The tumour was of a low-grade, so no adjuvant therapy was indicated. Regular follow-up (clinical and radiological) was proposed. The authors preferred an obturator prosthesis to a free flap reconstruction in order to facilitate clinical examination of the treated site. The patient's functional and aesthetic outcome is very satisfactory, with no speech or eating disorder. More than 2 years after treatment, the patient showed no local or distant recurrence.

Special care should be taken when encountering osteolytic lesions of the jaw, even in the presence of an impacted tooth.

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- **Ethical approval**: there was no need for the ethical approval for this case report
- **Informed consent**: there was no need for the informed consent for this case report as all the images were anonymized and no private data were provided allowing the patient's identification.

Authors contribution:

Author	Contributor role
Sibille Louis	Conceptualization, Investigation,Data curation, Writing original draft preparation, writing review and editing
Olszewski Raphael	Writing review and editing, Supervision
Magremanne Michele	Writing original draft preparation, writing review and editing, Supervision

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