

Mucoepidermoid carcinoma with metaplastic bone formation – A deceptive radiological presentation

SHORTEND TITLE: MEC with metaplastic bone – deceptive radiology

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Abstract

Mucoepidermoid carcinoma (MEC) is one of the most common primary salivary gland malignancies in both children and adults. MECs containing calcifications are rare, but well described in the literature. In contrast, there are only two case reports of MECs showing intra-tumoral bone formation. MECs associated with calcifications occur more frequently in minor salivary glands, compared to bone formation, which is more commonly seen in major glands. This possibly points to a different pathogenic mechanism. Calcifications of the head and neck region are generally diagnosed on conventional imaging by combining the anatomical location with the pattern of calcification. The

radiological findings of MECs containing calcifications or bone formation may mimic benign inflammatory processes such as sialoliths. The purpose of this paper is to report three additional cases of MECs containing metaplastic bone formation. These cases presented as painless swellings with radiological signs that could easily be mistaken for dystrophic calcifications. The clinical relevance of the paper is to make clinicians aware of the deceptive radiological appearance of this entity.

KEYWORDS: Salivary gland tumours, Mucoepidermoid carcinoma, Metaplastic bone, Maxillofacial Radiology, Oral and Maxillofacial Pathology

CLINICAL RELEVANCE STATEMENT

Mucoepidermoid carcinoma is one of the most common primary salivary gland malignancies in both children and adults. The purpose of this paper is to report three additional cases of MECs containing metaplastic bone formation. These cases presented as painless swellings with radiological signs that could easily be mistaken for dystrophic calcifications. The clinical relevance of the paper is to make clinicians aware of the deceptive radiological appearance of this entity.

INTRODUCTION

Salivary gland neoplasms represent 2.6% of all oral and maxillofacial lesions, with benign neoplasms being more prevalent than malignancies.¹ Mucoepidermoid carcinoma (MEC) is one of the most common primary salivary gland malignancies in both children and adults.¹⁻³ MEC represents 10% of all salivary gland neoplasms and 30% of salivary gland malignancies, with differing frequencies reported in different population groups.^{1,3} MECs are composed of squamoid, intermediate and mucous cells forming either cystic or solid tumours.² Several rare histologic variants exist, including sclerosing, clear cell and oncocytic.² MECs are graded histologically into low-, intermediate- and high-grade tumours based on the relative proportion of cell types, cystic areas and other quantitative features.⁴

MEC shows a slight female predilection and affects both children and adults with a wide age range (mean age: 48 years).^{1,3-5} MEC frequently involves the major salivary glands, with the parotid being the most frequently affected subsite.^{2,4,6} The palate and buccal mucosa are the preferred sites when the minor salivary glands are involved.^{2,4-6} An average reported clinical duration of 1.5 years has been reported in the literature.⁵ Clinically, MECs often present as slow-growing, asymptomatic swellings reaching a mean size of 4.5cm.¹ Rare reports of associated pain have been described in isolated cases.⁵ In contrast, high-grade tumours may present with rapid growth, paraesthesia and overlying mucosal ulceration.⁵ MEC involving the minor salivary glands may present as inconspicuous benign or inflammatory lesions, often mimicking mucoceles.⁵

Treatment often depends on the histologic grade⁴, but generally involves surgical removal of the tumour with at least 1cm clear margins.⁷ Due to their aggressive behaviour, high-grade tumours are often treated with adjunctive radiotherapy.⁷ The overall 5-year survival rate is reported between 94% and 67%, with a 5-year disease-free rate of 80%.^{8,9} Patient prognosis is influenced by the patient age, clinical stage of the disease, histologic grade and the anatomical subsite.^{8,9} Lower survival rates are reported in patients over 60 years of age, T3/T4 tumours, positive lymph nodes, high-grade tumours and submandibular or sublingual salivary gland involvement.^{8,9} The mean survival decreases from 110 to 75 months between low- and high-grade tumours.⁷

Conventional two-dimensional imaging is rarely used for the assessment of salivary gland tumours due to their soft tissue nature.¹⁰ Ultrasound in combination with magnetic resonance imaging (MRI) and/or computed tomography (CT) studies may be utilised to assess the circumscription of the tumour, identify areas of infiltration and evaluate lymph node involvement.¹⁰ In contrast, dystrophic salivary gland calcifications are often detected on conventional imaging with non-contrast CT exhibiting higher sensitivity.¹¹

MECs containing calcifications are rare, but well described in the literature.¹²⁻¹⁸ In contrast, there are only two case reports of MECs showing intra-tumoral bone formation.^{12,19} The purpose of this paper is to report three additional cases of MECs containing metaplastic bone formation. These cases presented as relatively painless swellings with radiological signs that could easily be mistaken for dystrophic calcifications secondary to an inflammatory process.¹⁹ The clinical relevance of this paper is to highlight the deceptive radiological appearance of this entity to treating clinicians.

CASE SERIES

Case 1

A 52-year-old male patient presented with a 3cm slow-growing mass of unknown duration involving the right buccal mucosa. The patient reported no co-morbidities. On intraoral examination, the overlying mucosa appeared normal, with no ulceration detected. A panoramic radiograph only revealed small speck-like calcifications overlying the right mandibular ramus (Figure 1). Unfortunately, no advanced imaging was performed in this case. The buccal swelling was excised and submitted for histological assessment. The final diagnosis was an oncocytic variant of mucoepidermoid carcinoma, intermediate-grade, containing calcifications and metaplastic bone formation. The tumour was completely excised and the patient subjected to regular follow-up appointments.

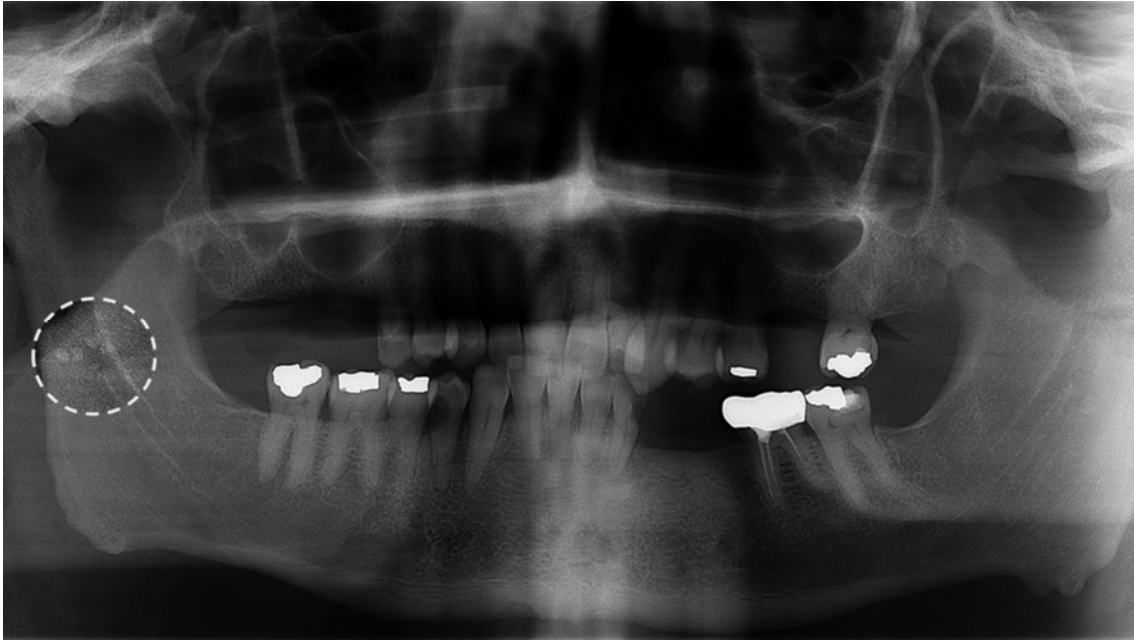


FIGURE 1: Panoramic radiograph of Case 1 showing small speck-like calcifications overlying the right ramus (encircled).

Case 2

A 53-year-old healthy female patient presented with a three-year history of a slow-growing mass involving the left submandibular region. The mass was intermittently painful and failed to resolve following numerous courses of antibiotics. A panoramic radiograph revealed multiple calcified bodies overlying the left posterior corpus and angle of the mandible (Figure 2). Cone-beam computed tomographic (CBCT) imaging showed that the calcified bodies were located lingual to the left ramus, corresponding to the area of the submandibular salivary gland (Figure 3). The calcifications were arranged in a circular pattern. The superficial and deep lobes of the submandibular salivary gland were excised and submitted for histological assessment. The final diagnosis was a high-grade mucoepidermoid carcinoma with extensive metaplastic bone formation. Due to the extensive perineural infiltration, the patient was referred for adjunctive radiotherapy. The patient was subjected to regular follow-up appointments.



FIGURE 2: Panoramic radiograph of Case 2 showing irregular calcifications superimposed over the left mandibular angle (encircled).

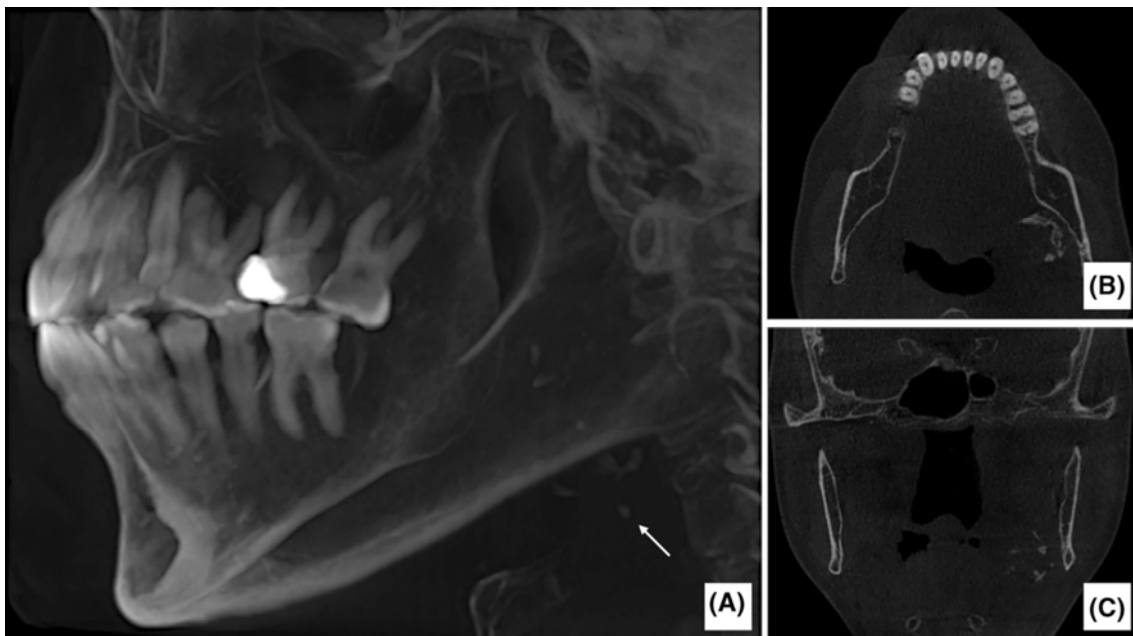


FIGURE 3: (A) Three-dimensional reconstructed, (B) axial and (C) coronal CBCT images of Case 2 showing circular calcifications involving the lingual surface of the left ramus corresponding to the site of the submandibular salivary gland.

Case 3

A 52-year-old male patient, who was human immunodeficiency virus (HIV)-positive, presented with a two-year history of a firm mass involving the left sublingual region. The patient's other medical

history included diabetes mellitus and hypertension, both controlled via medication. Unfortunately, no radiographic imaging was performed. The sublingual salivary gland was excised and submitted for histological examination. The final diagnosis was an intermediate-grade mucoepidermoid carcinoma with metaplastic bone formation. The tumour was completely excised and the patient subjected to regular follow-up appointments.

HISTOPATHOLOGICAL FINDINGS

All three cases in this series showed similar features of a solid to cystic tumour comprising of epidermoid, intermediate and mucous cells (Figure 4 A–C). Cases 1 and 3 were classified as intermediate-grade tumours showing a mild-to-moderate degree of cytologic atypia with occasional mitotic figures and an infiltrative growth pattern. The vast majority of tumour cells in Case 1 showed prominent, granular cytoplasm with nuclear pleomorphism and large central nucleoli, indicative of oncocytic change. Case 2 showed high-grade cytologic atypia with abundant mitoses, areas of necrosis, small nests and islands at the invasive front and perineural infiltration. Of note, all three tumours contained varying degrees of intra-tumoral metaplastic bone, ranging from isolated (Cases 1 and 3) to extensive (Case 2). In addition, Case 1 showed scattered intra-tumoral calcifications.

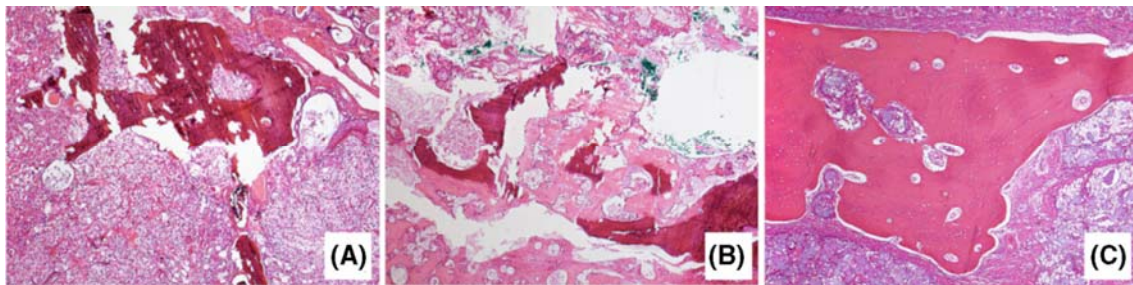


FIGURE 4: Representative haematoxylin and eosin (H&E)-stained sections of (A) Case 1, (B) Case 2 and (C) Case 3 showing mucoepidermoid carcinomas with varying degrees of intra-tumoral metaplastic bone formation (original magnifications x 200).

DISCUSSION

Calcifications of the head and neck region are generally diagnosed on conventional imaging by combining the anatomical location with the presenting clinical features and pattern of calcification.²⁰ The radiological findings of MECs containing calcifications or bone formation may mimic benign inflammatory processes such as sialoliths.²¹ In particular, the radiological features of Case 1 may mimic tonsiliths, which usually present as multiple oval to round radiopacities overlying the ascending ramus.²⁰ The clinical presentation and radiological features of Case 2 may easily be misinterpreted as intraparenchymal sialoliths involving the submandibular gland.²⁰ Sialoliths are frequently accompanied by clinical swelling and intermittent pain, often presenting as oval or

elongated calcifications overlying the mandibular angle.²⁰ However, cases with similar radiological signs may reveal more sinister diagnoses.²¹

Intra-tumoral calcifications associated with MEC are rare, with only 12 cases reported in the literature.¹²⁻¹⁸ MECs with associated calcifications appear to arise more frequently in the conventional and clear cell variants, mostly involving the minor salivary glands of the palate.¹³ Only one case of MEC with calcifications has been reported in the parotid gland.¹³ Four proposed theories were suggested for the occurrence of these calcifications.¹⁵ Yoon *et al.*, postulated that these calcifications formed part of the tumoral component or resulted from metastatic calcifications secondary to hypercalcaemia.¹⁵ Dystrophic calcification of necrotic areas within the tumour has also been proposed as a possible mechanism.^{12,15} It has been found that these calcifications tend to occur regardless of tumour grade and are seen in increased frequencies in low-grade tumours.¹³ Low-grade tumours per definition do not contain areas of necrosis, making the aforementioned theory seem less likely. Finally, calcifications may occur due to dystrophic calcification of mucin secreted by the tumour cells.^{12,15} This concept has received the most support and has been reinforced by immunohistochemical investigations.¹⁶ This theory may best explain the high prevalence of calcifications seen in minor salivary gland tumours, having thicker mucinous secretions compared to major salivary glands.¹³

Bone formation within salivary gland tumours has been previously reported in pleomorphic adenomas.²²⁻²⁴ MEC with intra-tumoral bone formation has only been reported in two previous cases.^{12,19} The clinicopathological details of these cases are summarised in Table 1 together with the additional cases documented in this report. Interestingly, bone formation within MECs was up until now only reported in major salivary glands, in particular the sublingual gland. This series includes the first case of MEC with intra-tumoral bone formation in minor salivary glands. In the case described by Maruse *et al.*, the authors speculated that the areas of dystrophic calcification formed the substrate for osteoid organisation.¹² This finding was also noted in a separate case report where osteoid formation was noted in a sialolith.²⁵ Bone formation associated with calcifications was also seen in Case 1 of the current series. Secondly, the authors postulated that bone formation may result from endochondral ossification or metaplasia of stromal cells into osteoblasts.¹² In the second reported case by Wolf *et al.*¹⁹, the authors concur with the theory that a metaplastic mechanism may be responsible for the bony formation. The authors of the current paper agree with this postulate, however, further research is required to support this hypothesis.

TABLE 1: Reported cases, including the current series, of mucoepidermoid carcinomas with metaplastic bone formation

Case	Age/ Gender	Clinical signs and symptoms	Medical History	Location	Clinical duration (months)	Radiological findings	Histological diagnosis
Maruse <i>et al.</i> 2015 ¹²	75 F	Asymptomatic swelling	Diabetes mellitus and hypertension	Sublingual gland	2	Well- circumscribed mass in the sublingual region with calcifications	MEC with ectopic bone formation intratumorally
Wolf <i>et al.</i> 2020 ¹⁹	48 F	Swelling with intermittent pain	Diabetes mellitus and hypertension	Sublingual gland	12	Enlargement of the sublingual gland with central calcifications	Low-grade MEC with intra-tumoral bone formation
Case 1	52 M	Localised asymptomatic swelling	Healthy	Minor salivary glands of the buccal mucosa	Unknown	Small speck-like calcifications overlying the mandibular ramus	Intermediate- grade MEC (oncocytic variant) with metaplastic bone
Case 2	53 F	Swelling with intermittent pain	Healthy	Submandibular gland	36	Irregular calcifications arranged in a circular pattern located in the region of the submandibular salivary gland	High-grade MEC with metaplastic bone
Case 3	52 M	Asymptomatic swelling	Retroviral disease, diabetes mellitus and hypertension	Sublingual gland	24	Not available	Intermediate- grade MEC with metaplastic bone

F: Female, M: Male

Interestingly, calcifications associated with MECs occur more frequently in minor salivary glands, compared to bone formation, which is more commonly seen in major glands. This possibly points to a different pathogenic mechanism. The cases reported in the literature, including this case series, had an inconspicuous presentation of asymptomatic swellings, with some patients describing intermittent pain. MECs with metaplastic bone presented at a mean age of 56 years, with a near equal gender distribution. MECs with associated calcifications seem to occur at a younger mean age of 44 years, with females twice as commonly affected. Metaplastic bone formation occurred in all grades of

MECs, similar to cases containing calcifications. It is unknown why the majority of MECs with metaplastic bone formation occurred in patients with comorbidities, including diabetes mellitus and hypertension. These coexisting conditions could be an unrelated finding associated with advanced age.

The limitations of this paper include the absence of imaging in case 3, advancing imaging in case 1, and a lack of adequate patient follow-up. In conclusion, due to the rarity of these findings, increased publications of such cases may assist in deducing the clinical relevance of these findings. At this stage it seems metaplastic bone formation does not influence treatment or patient prognosis. The importance of these radiological features should however be highlighted to raise awareness among clinicians.

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