# Multiple calcifying epithelial odontogenic tumor: case report and review of the literature

Ana Carolina Hanaoka Ibituruna, DDS,[a] Anaíra Ribeiro Guedes Fonseca Costa, DDS, PhD student,[b] Luiz Fernando Barbosa de Paulo, DDS, MSc, PhD,[c] Paulo Rogério de Faria, DDS, MSc, PhD,[d] Sérgio Vitorino Cardoso, DDS, MSc, PhD,[e] and Adriano Mota Loyola, DDS, MSc, PhD[f]

Calcifying epithelial odontogenic tumor (CEOT) is a rare benign neoplasm, and few cases of multiple lesions have been published. This article reports the case of a 26-year-old male patient with bilateral gingival lesions near the maxillary canines and a hard tumor on the left side of the mandible. All lesions presented mixed radiographic appearance (radiolucent and radiopaque). Incisional biopsies revealed typical histopathologic findings of CEOT. The gingival lesions were removed by curettage, and the mandibular tumor was surgically resected. No recurrence was detected after 6 years of treatment. Five well-documented cases of multiple CEOT were retrieved from the PubMed database. These patients were slightly older than those with solitary tumors, and none of them presented syndromic features. Three cases had only multiple central tumors, and the other 2 had multiple peripheral lesions, so the present patient is the first to manifest with both central and peripheral tumors. (Oral Surg Oral Med Oral Pathol Oral Radiol 2019;128:268–272)

Calcifying epithelial odontogenic tumor (CEOT) is a rare epithelial benign odontogenic tumor that accounts for less than 1% of all odontogenic tumors.[1] Thoma and Goldman[2] first described CEOT in 1946, but it was only acknowledged as a distinct entity by Pindborg[3] in 1958. The tumor affects both sexes equally, with a peak incidence in the third and fourth decades of life.[4–7] CEOT is considered a locally aggressive lesion, with reports of malignant transformation.[7]

Nearly 90% of the CEOTs occur as intraosseous lesions, and the mandible is more frequently affected compared with the maxilla.[1,7,8] Although central CEOT is more common in the premolar–molar area, peripheral tumors are more commonly found in the canine–incisor region. This tumor usually manifests as an asymptomatic, slow-growing swelling. Radiographically, CEOT can manifest as a unilocular or multilocular radiolucency, with radiopaque spots found in nearly 75% of the cases. Additionally, half of all tumors are associated with unerupted teeth.[7,9]

Microscopically, CEOT is composed of polyhedral epithelial cells with eosinophilic cytoplasm, hyperchromatic nucleus, and indistinct nucleoli, arranged in islands, chords, or large sheets.[1] Mitotic figures are rare; perineural and vascular invasion are absent, but anisocytosis and anisokaryosis are typically found in this tumor.[1,7,8] Extracellular deposits of lightly eosinophilic amorphous material (amyloid odontogenic ameloblast-associated protein) of apple-green birefringence can be found in the tumor stroma, as well as concentric calcified rings (Liesegang rings).[1] Clear-cell, Langerhans cell, and cystic variants have also been described.[2,9–12]

CEOT is usually treated with surgery. Perforation or erosion of the cortical bone are signs of aggressive behavior and, therefore, indicate marginal or segmental resection to reduce the risk of recurrence in peripheral and central tumors, respectively.[1,9,10] Recurrence rates vary from 0% to 20%, being high in cases conservatively treated and in peripheral lesions.[7,8]

Few cases of multiple CEOT can be found in the literature.[11,13–16] The primary purpose of this report was to describe the case of a patient with multiple, synchronous CEOTs and to discuss the main features of this condition. Differences between solitary and multiple lesions are also addressed with respect to their clinicopathologic aspects, biologic behavior, and prognosis.

## CASE REPORT

A 26-year-old white male patient was referred to the Dental Hospital of our University for assessment of an asymptomatic gingival swelling. Extraoral examination revealed a mild swelling on the left side of the mandible. Intraoral aspect consisted of 2 bilateral sessile, well-circumscribed nodules in the region of both canines, measuring 15 mm and 20 mm, respectively. An expansive intraosseous lesion was also seen on the left side of the mandible, which exhibited bicortical growth and displacement of teeth from the lateral incisor to the first molar (Figure 1).

[a]Fellow of the Department of Oral and Maxillofacial Pathology, Federal University of Uberlândia, Uberlândia-MG, Brazil.
[b]Department of Oral and Maxillofacial Pathology, Federal University of Uberlândia, Uberlândia-MG, Brazil.
[c]Department of Oral and Maxillofacial Surgery, Dentistry Hospital, Federal University of Uberlândia, Uberlândia-MG, Brazil.
[d]Department of Morphology, Biomedical Sciences Institute, Federal University of Uberlândia, Uberlândia-MG, Brazil.
[e]Department of Oral and Maxillofacial Pathology, Federal University of Uberlândia, Uberlândia-MG, Brazil.
[f]Department of Oral and Maxillofacial Pathology, Federal University of Uberlândia, Uberlândia-MG, Brazil.
Received for publication Nov 21, 2018; returned for revision Mar 6, 2019; accepted for publication Mar 19, 2019.

2212-4403/$-see front matter
https://doi.org/10.1016/j.oooo.2019.03.018

Panoramic radiography showed a mild radiolucency in the region of the left maxillary lesion. In the mandible, the lesions were mixed radiopaque−radiolucent with well-circumscribed limits. Cone beam computed tomography revealed cortical and bone marrow erosions, and hyperdense particles inside both peripheral lesions. The intraosseous lesion in the mandible was predominantly hypodense, but hyperdense areas representing mineralized material were also observed. The buccal and lingual bone plates were perforated (Figure 2).

The synchronous occurrence and similar imaging features suggested that all lesions had the same origin and pathogenesis. Their development in the tooth-bearing areas with mixed radiolucent−radiopaque aspects indicated an odontogenic nature. Differential diagnosis included multiple synchronous mixed odontogenic tumors, mainly calcifying epithelial odontogenic tumor, calcifying cystic odontogenic tumor, and ameloblastic fibro-odontoma.

On the basis of these hypotheses, incisional biopsies under local anesthesia were performed so that specimens from all lesions could be collected in a single session. The tissue fragments were fixed in 10% formalin. Microscopic examination of hematoxylin and eosin−-stained slides confirmed that all lesions had the same composition: polyhedral epithelioid neoplastic cells of variable size, with clear and lightly eosinophilic cytoplasm (Figure 3). Some cells showed mild atypia (anisocytosis, anisokaryosis, and nuclear hyperchromasia). Multinucleated cells were occasionally seen. Tumor stroma was composed of dense irregular connective tissue, with the foci of amorphous Congo red-positive amyloid-like deposits showing apple-green birefringence under polarized microscopy. Some basophilic calcified deposits (Liesegang rings) were also seen. These findings led to the diagnosis of multiple CEOTs.

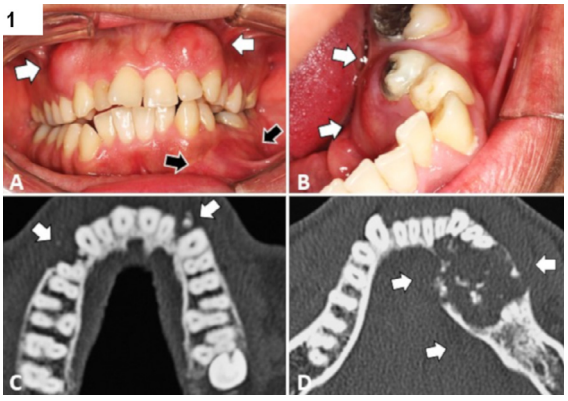


Fig. 1. Clinical aspect of a patient with multiple calcifying epithelial odontogenic tumor (CEOT). **(A)** Bilateral gingival swelling in the anterior maxilla *(white arrows)* and expansion of the buccal plate in the mandible *(black arrows)*. **(B)** Bicortical expansion of the mandible with tooth displacement from the left lateral incisor to the first molar *(white arrows)*. Cone beam computed axial tomography images of the case. **(C)** Hypodense lesion with hyperdense material and disruption of the vestibular cortical bone in both maxillary lesions *(arrows)*. **(D)** Similar aspect with bicortical bone expansion in the mandible tumor *(arrows)*.

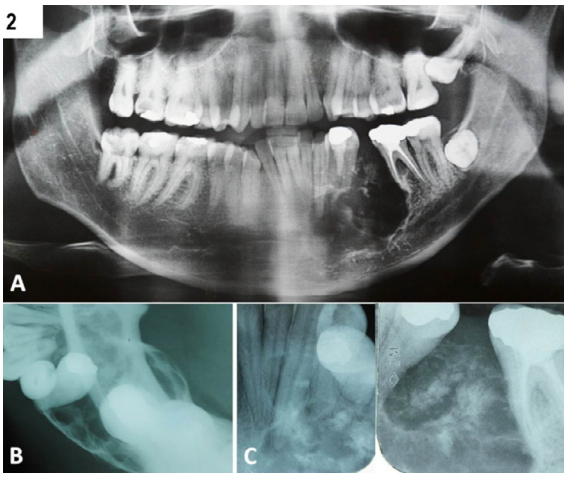


Fig. 2. Radiographic aspects of the case. **(A)** Panoramic radiography shows a well-defined radiolucent lesion with corticated borders in the left mandibular body. **(B)** Occlusal radiography showing multilocular bicortical expansion without apparent cortical perforation. **(C, D)** Periapical radiographs showing the lesion with well-circumscribed borders and radiopaque content.

The patient was submitted to a surgical procedure under general anesthesia to remove the lesions in a single session. Both peripheral CEOTs were curetted, and the adjacent bone was removed by using rotary drill maxicut in the low-speed handpiece to reduce the risk of recurrence. Extraoral submandibular access was performed to remove the mandibular tumor with surgical margins of 1 cm with a reciprocating saw. A 2.4-mm locking titanium plate was immediately fixed (Figure 4), and the surgical specimens were again submitted for histopathologic analysis. The same microscopic aspects were observed as in the previous slides, thus confirming the diagnosis of multiple CEOTs. No recurrence was observed in the first 24 months of follow-up.

After the follow-up period, mandibular reconstruction procedure with free iliac crest bone grafting was conducted, using the same extraoral access for the tumor resection. The titanium plate was removed, and the bone graft was positioned in a 2-mm fixation plate (see Figure 4). The patient has been followed up for more than 72 months and has shown no evidence of recurrence. He is awaiting functional and aesthetic rehabilitation with osseointegrated implants.

## LITERATURE REVIEW

Six cases of multiple CEOTs were retrieved from the PubMed database[11,13−17] One of these articles reported a case of 2 allegedly distinct variants (central

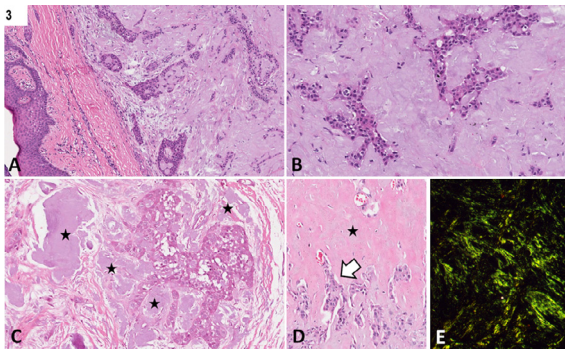


Fig. 3. Histopathologic aspects of the case. **(A)** Peripheral lesions were well-circumscribed and separated from the connective tissue by an apparent absence of fibrous capsule *(arrows)*. Tumor islands were immersed in homogeneous amphiphilic matrix that represents amyloid *(asterisks)* (hematoxylin and eosin [H&E]; original magnification × 200). **(B)** Details of epithelial islands of the tumor parenchyma (H&E; original magnification × 40). **(C)** Details of the mandibular lesion showing amyloid material inside and outside the tumor islands *(arrows)* (H&E; original magnification × 200). **(D)** Eosinophilic dentinoid material *(asterisks)* with cell inclusions involving tumors islands *(arrows)* (H&E; original magnification × 400). **(E)** amyloid material stained with Congo red showing apple-green birefringence under polarized light microscopy (original magnification × 400). High resolution versions of the following slides for use with the Virtual Microscope are available as eSlides: (A) *VM05570 and VM05572*; (C) *VM05573*

and peripheral) of CEOT, but that article was excluded from the present review because the bone and soft tissue lesions in the reported case were contiguous.[17] The final selection included 5 cases published in different articles between 1984 and 2012. Their main clinicopathologic and therapeutic features are summarized in Tables I and II. Each patient had 2 to 4 lesions, which were always synchronous. Three of these previous cases presented as multiple central tumors, and 2 patients had only peripheral lesions, so the present case is the first to have central and peripheral lesions simultaneously. Interestingly, 1 study reported a patient with a squamous odontogenic tumor and 2 reported intraosseous mandibular CEOTs.[15]

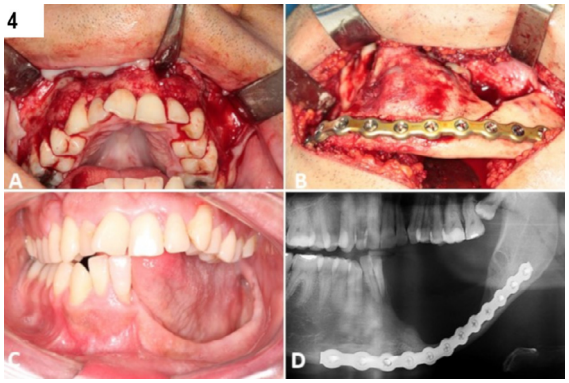


Fig. 4. Aspects of the surgical resection of the peripheral and central tumors. **(A)** View of the peripheral lesions and their topographic relationship with the cortical bone. **(B)** Tumor resection followed by immediate fixation of the titanium plate. **(C)** Intraoral aspects 24 months after surgical intervention. **(D)** Panoramic radiography showing mandibular reconstruction with iliac crest bone grafting and fixation plate.

## DISCUSSION

This report describes a rare case of multiple CEOTs and a summary of the knowledge on the clinicopathologic, behavioral, and therapeutic aspects of this condition.

According to our literature review, many CEOTs bear no sex predilection as in the case of solitary tumors. Most patients are older than 40 years of age, being slightly older than the average age for solitary tumors.[7] This report describes the case of the youngest patient with multiple CEOTs reported in the literature so far. Similar to solitary CEOT, multiple tumors are usually asymptomatic bone swellings. Only 1 patient with numerous peripheral mandibular CEOTs complained of pain.[14] The majority of central solitary tumors appear in the mandibular body, whereas solitary peripheral tumors are more frequent in the anterior maxilla and the mandible.[7] In patients with multiple CEOTs, the distribution between the maxilla and the mandible or between the anterior and posterior regions are not specific.[7,8] Central tumors are larger than peripheral tumors in both variants, probably because of their insidious growth inside bone. Three of the 6 patients with multiple CEOTs had peripheral lesions.[11,14] This ratio is high in comparison with solitary cases (approximately 10%).[7]

Mixed radiographic aspects, cortical expansion, and tooth displacement are common findings in both solitary and multiple CEOTs. However, an association with unerupted teeth is rare.[1,7,8] Histopathologically, there is no difference between multiple and solitary CEOTs.

When cortical bone is affected, nonconservative surgical approaches are indicated to reduce relapse of solitary CEOTs.[1,7] The 2 largest lesions in our review were resected and did not recur after prolonged follow-up.[15] This includes the mandibular lesion in the present case, which had the longest follow-up. One previous case of bilateral peripheral mandibular CEOT recurred after surgical excision.[14] Another patient developed 2 consecutive local recurrences of an initially small, maxillary CEOT treated with conservative surgery. The recurrences were followed by de novo tumors in the maxilla and the mandible.[14,16] These findings suggest that conservative surgery should be employed with great caution for multiple CEOTs, even when cortical perforation is not evident.

Recurrence of CEOT can result in malignant transformation, with molecular aberrations, prominent cytologic atypia, massive growth, local invasion, and metastatic spread to cervical lymph nodes and distant sites.[18–20] In

**Table I.** Demographic, clinicopathologic, and radiographic aspects of the multiple CEOT cases found in the literature

| *Authors, year* | *Age (years)* | *Gender* | *No. of lesions** | *Location (C/P)* | *Dimension(cm)* | *Symptomatology* | Rx† |
|---|---|---|---|---|---|---|---|
| Chomette et al., 1984 | 40 | F | 2 | Mx [14,25] (C)<br>Md [18,17] (C) | Mx = 3<br>Md = 3 | Asymptomatic | Mixed; unilocular<br>Third molar unerupted |
| Sedghizadeh et al., 2007 | 68 | M | 4 | Mx [9];[13];[14] (C)<br>Md [20] (C) | NR[5] | Asymptomatic | Mixed, unilocular |
| Abrahão et al., 2009 | 40 | F | 2 | Md [19,20]; [44,45] (P) | NR | Pain | — |
| Oliveira et al., 2009 | 43 | F | 2 | Mx [12-15]; Md [18,29] (P) | Mx = 2<br>Md = 2 | Asymptomatic | — |
| Tarsitano et al., 2012 | 55 | M | 2 | Mx [6-8]; Md [22-29] (C) | Mx = NR;<br>Md = 5 | NR | Radiolucent, multilocular |
| Ibituruna et al., 2017 (present case) | 26 | M | 3 | Mx [6];[11] (P)<br>Md [19-22](C) | Mx = 1,5 e 2,0<br>Md = 7 | Asymptomatic | Mixed, multilocular |

*Teeth identified using Universal Numbering System.
†Radiographic aspects; mixed = radiolucent and radiopaque.
*C,* central; *CEOT,* calcifying epithelial odontogenic tumor; *F,* female; *M,* male; *Md,* mandible; *Mx,* maxilla; *NR,* not reported; *P,* peripheral.

**Table II.** Treatment and follow-up data distribution of patients diagnosed with multiple CEOTs

| *Authors, year* | *Bone erosion/cortical perforation* | *Surgical procedure* | *Follow-up period (months)* | *Recurrences* |
|---|---|---|---|---|
| Chomette et al., 1984 | NR | Enucleation | NR | NR |
| Sedghizadeh et al., 2007 | NR | Enucleation with margins | NR | NR* |
| Abrahão et al., 2009 | Bilateral bone erosion (mx at 12-month recurrence) | Excision/bone curettage | 42 | YES |
| Oliveira et al., 2009 | Bone erosion (mx) | Excisional biopsy | 12 | Absent |
| Tarsitano et al., 2012 | Bone erosion (mx and md) | Mx − enucleation<br>Md − resection/segmental osteotomy | 42 | Absent |
| Ibituruna et al., 2017 (case reported) | Bilateral bone erosion (mx); cortical perforation (md) | Mx − excision/bone curettage<br>Md − resection/segmental osteotomy | 72 | Absent |

*In this case, two previous recurrences were informed by the patient during the appointment.
*CEOT,* calcifying epithelial odontogenic tumor; *Md,* mandible; *Mx,* maxilla; *NR,* not reported.

the present case, the possibility of metastatic spread to multiple sites was considered negligible, given the typical cytologic appearance, the synchronous occurrence, and the relatively slow growth of the lesions.

Odontogenic tumors may be part of the spectrum of syndromes, and this situation favors the occurrence of multiple tumors. Examples include multiple odontomas (and osteomas) in Gardner,[21,22] otodental,[23] esophageal stenosis, or epidermal nevus syndrome,[24] and ameloblastoma in Gorlin-Goltz syndrome.[25] None of the patients with multiple CEOTs presented syndromic features.

## CONCLUSIONS

CEOT should always be considered an aggressive odontogenic tumor because of its increased risk of recurrence, malignant transformation, and development of de novo lesions. Nonconservative surgical treatment must be considered even for small lesions, and prolonged follow-up is mandatory.

## DISCLOSURE

This research was supported by FAPEMIG (Fundação de Amparo à Pesquisa de Minas Gerais) [grant No. #3053/15] and CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, Brasil) [finance code 001].

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*Reprint requests:*

Adriano Mota Loyola
Department of Oral and Maxillofacial Pathology
Federal University of Uberlândia
Rua Pará, 1720, Umuarama
Uberlândia-MG
Brazil 38405-302.
loyolaam@gmail.com