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CASE REPORT

# Clear-cell variant of calcifying epithelial odontogenic tumor (Pindborg tumor) in the mandible

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**We present an uncommon case (female patient aged 59 years) of the clear-cell variant of calcifying epithelial odontogenic tumor (CEOT) (also known as Pindborg tumor) in the mandible. The clinical characteristics and probable origins of the clear tumor cells of previously reported cases of clear-cell variant of intraosseous CEOT are also summarized and discussed.**
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## INTRODUCTION

Calcifying epithelial odontogenic tumor (CEOT) (also known as Pindborg tumor), which was first designated as a distinct disease entity by Pindborg, is an uncommon benign odontogenic lesion that accounts for less than 1% of all odontogenic tumors. It most often occurs in the posterior mandible and is most frequently found in patients between 30 and 50 years of age, with no sex predilection.[1] In addition to the intraosseous lesion, a number of extraosseous counterparts of CCEOT have also been documented.[1] Clinically, CEOT is usually a slow-growing painless swelling. Radiographically, a unilocular radiolucency destructive lesion is observed. The classical histopathological characteristics of CEOT comprise sheets and islands of polyhedral eosinophilic epithelial cells with calcifications as well as deposition of an amyloid-like substance; however, occasionally, focal areas of clear cells can be observed in the clear-cell variant of CEOT (CCCEOT).[2]

Through a MEDLINE search for CCCEOT in the English-language literature (1967–2011), 14 cases were found;[3–16] however, this unusual lesion still needs continual documentation in order to have more information regarding clinical, microscopic features or behavior, particularly, the potential origins of the clear tumor cells. Therefore, the aim of the current report was to describe the clinical, radiographic, and histological findings in a case of mandibular CCCEOT. The clinical features as well as the potential origins of the clear tumor cells of previously reported cases of intraosseous CCCEOT are reviewed.

## CASE REPORT

A 59-year-old female was referred for evaluation of a painless swelling over the left retromolar area. The patient's medical history was significant for the diagnosis of hypertension. Intraoral examination showed a hard, non-tender 3 cm×2 cm mass on the lingual aspect of the left retromolar area up to half of the mandibular ramus. The overlying mucosa was intact (Figure 1a). A panoramic radiograph showed a well-defined unilocular radiolucence with a corticated margin extending from the distal root of tooth 38 up to half of the left ramus area, and from the left retromolar area down to the mandibular body, which measured about 3 cm×2 cm in diameter (Figure 1b). The differential diagnosis included keratocystic odontogenic tumor, ameloblastoma, ameloblastic fibroma and CEOT. An incisional biopsy was performed under local anesthesia. The specimen was sent to the Oral Pathology Department of our institution for histological examination. Microscopic examination of the incisional biopsy showed that a large portion of the tumor was arranged in a pseudoglandular pattern consisting of nests of pale, uniform, clear cells with dark-stained nuclei without abnormal mitotic figures and necrosis (Figure 2a), whereas some areas were admixed with clusters of polyhedral epithelial cells (Figure 2b). The cells were separated by thin bands of connective tissue in areas showing deposits of amorphous eosinophilic material. Small foci of calcifications were also noted, but no Liesegang rings were observed (Figure 2c). Staining was negative for periodic acid fast stain (PAS) stains with and without diastase digestion (data not shown), as well as mucicarmine stain (data not shown), but positive for Congo red stain throughout the intercellular eosinophilic material (Figure 3a). With regard to immunohistochemical stainings, the tumor cells were positive for cytokeratin only (Figure 3b), and negative for S-100 protein (Figure 3c) and smooth muscle actin (Figure 3d). The findings for Ki-67 were positive in only a small number of scattered cells (Figure 3e). Therefore, the histological diagnosis was CCCEOT.

The swelling was then removed under general anesthesia. Similar microscopic findings to the incisional biopsy were observed for the surgical specimen (Figure 2d). The histological diagnosis of the surgical specimen was confirmed again to be CCCEOT. The postoperative course of the patient was uneventful, and there was no evidence of disease at the 2-year follow-up.

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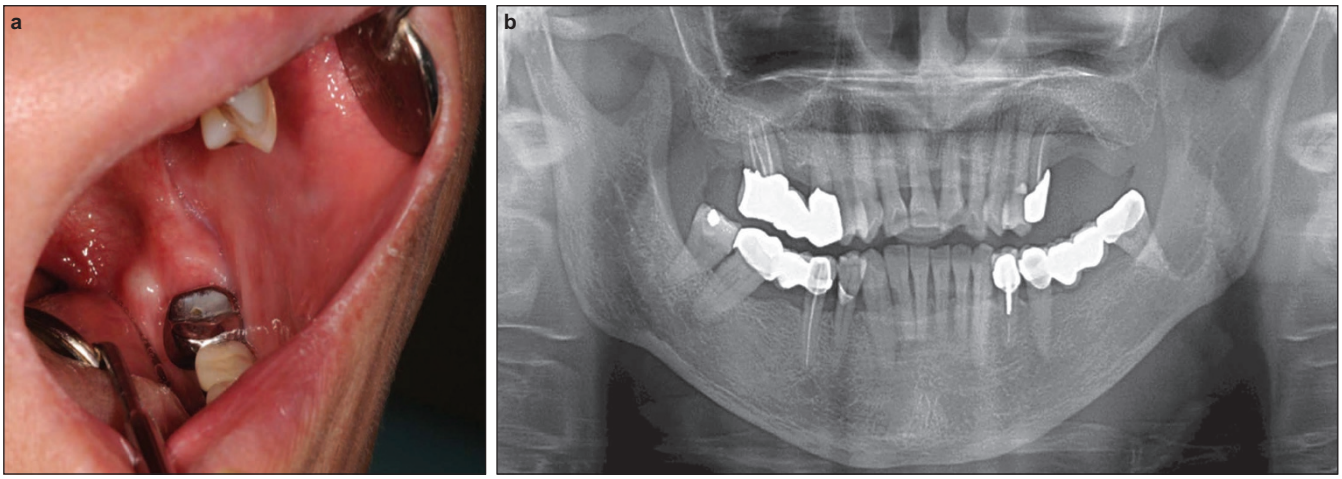


**Figure 1 Intraoral view and panoramic radiography.** (**a**) Intraoral examination showed a mass on the left retromolar area up to half of the mandibular ramus. (**b**) Panoramic radiograph showed a well-defined unilocular radiolucence with a corticated margin extending from the distal root of tooth 38 up to half of the left ramus area, and from the left retromolar area down to the mandibular body.

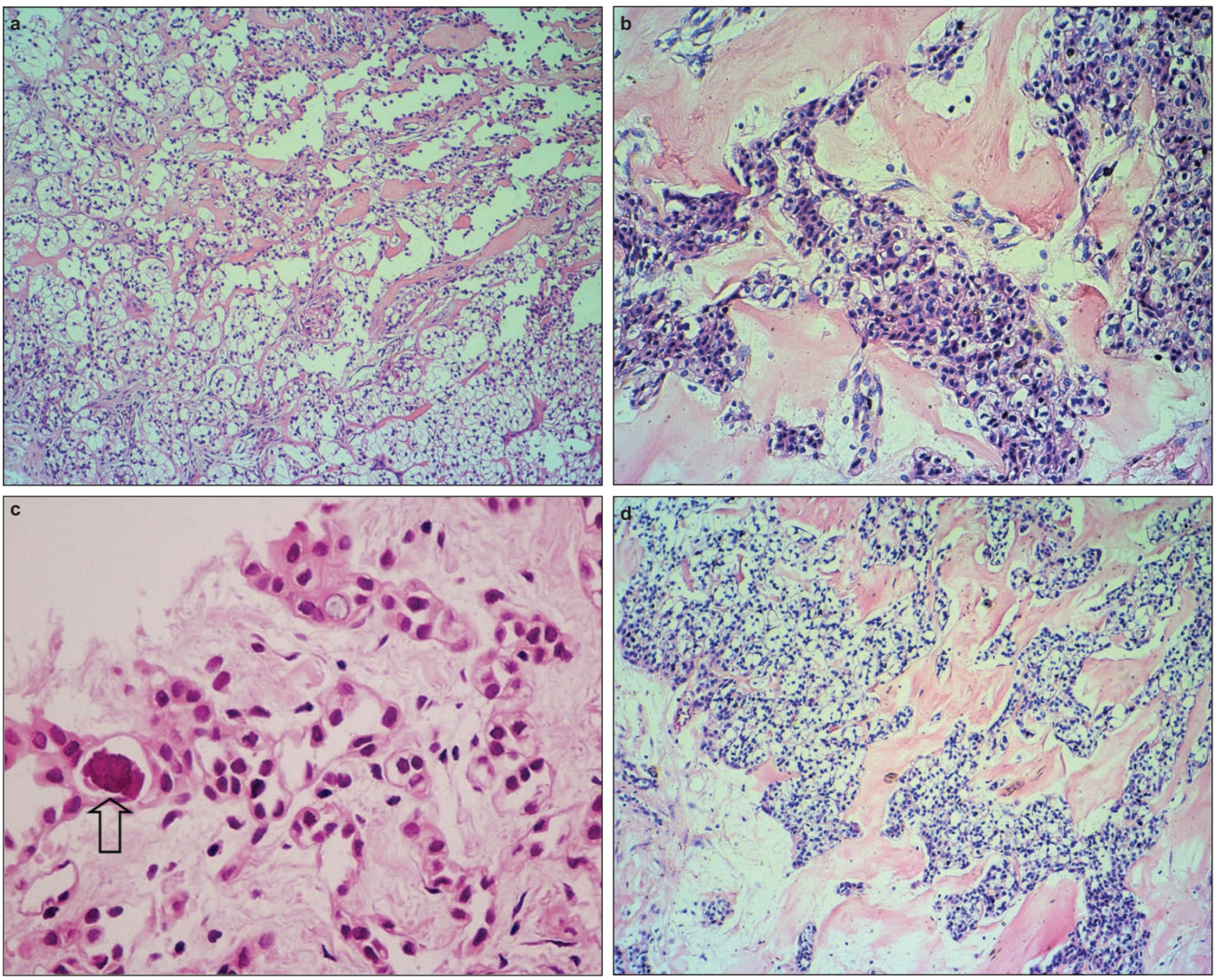


**Figure 2 Histological aspects of the incisional and excisional biopsies.** Incisional biopsy showed that a large portion of the tumor was arranged in a pseudoglandular pattern consisting of nests of pale, uniform, clear cells with dark-stained nuclei (**a**, ×40), whereas some areas were admixed with polyhedral epithelial cells (**b**, ×100) and contained small foci of calcification (arrow, **c**, ×200). (**d**) Similar histopathological findings to the incisional biopsy were observed for the surgical specimen (×40).

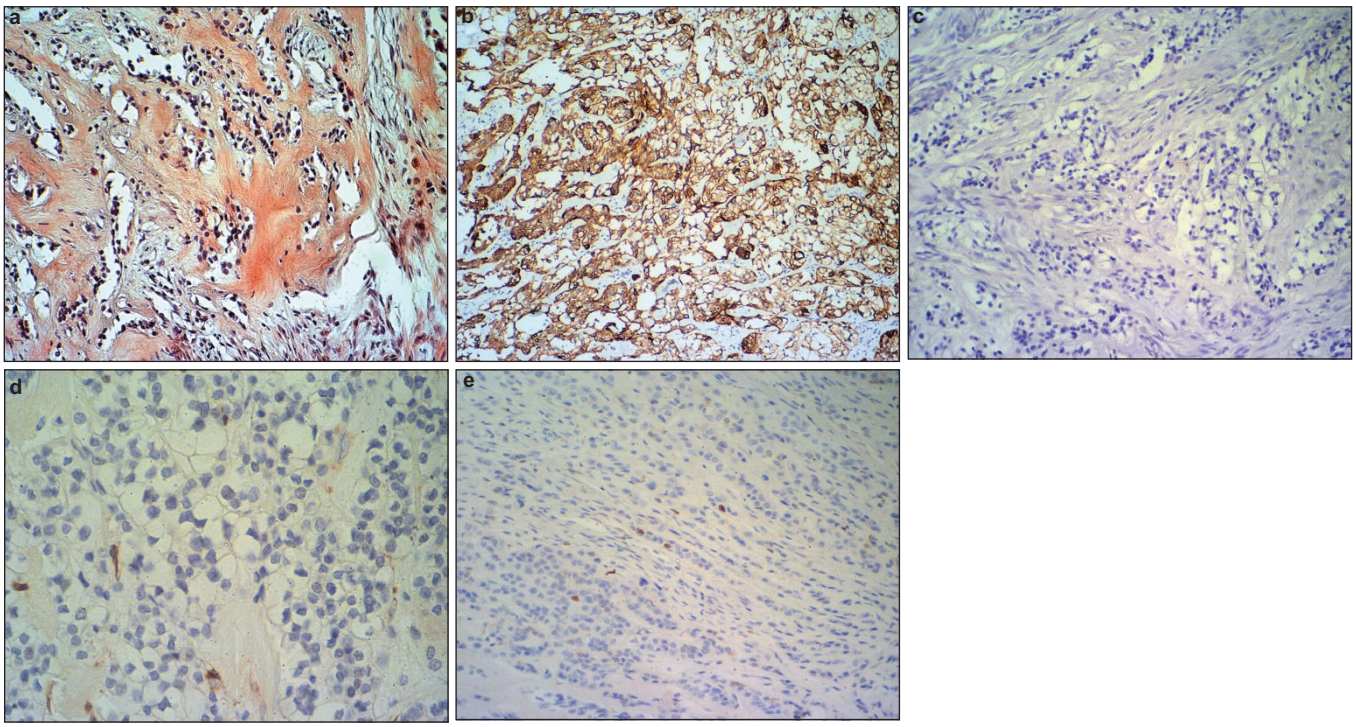


**Figure 3 Histochemical and immunohistochemical aspects.** Staining was positive for Congo red stain for the intercellular eosinophilic material (**a**, ×200). The tumor cells were positive for immunochemical staining of cytokeratin (**b**, ×100), negative for S-100 (**c**, ×100) and smooth muscle actin (**d**, ×200) as well as low Ki-67 labeling index (**e**, ×100).

## DISCUSSION

The histopathology of CEOT, in its classic pattern, comprises sheets of polyhedral epithelial cells with well-defined cell borders and distinct intercellular bridges; these neoplastic cells may demonstrate pleomorphism, but only rarely typical mitoses. Additionally, the other most characteristic findings are the presence of amyloid-like substances and calcified concentric Liesegang rings. To date, five histopathologic patterns of CEOT have been documented:[17–18] (i) strands/sheets/islands of polyhedral cells with intracellular bridges; (ii) a cribriform arrangement with many spaces containing an eosinophilic (amyloid-like) substance; (iii) densely-populated neoplastic cells with interspersed multinucleated giant cells; (iv) nests of epithelial cells similar to neoplasm of the salivary gland; and (v) prominent clear-cell arranged in a pseudoglandular manner. The last pattern is referred to as the clear-cell variant of CEOT, and the histopathological findings of the current case were consistent with this pattern, showing abundant clear cells arranged in a pseudoglandular pattern containing an amyloid-like material.

In the current case, a relatively high proportion of the clear tumor cell components were observed. The diagnosis of CCCEOT in the present case was reached according to the positivity of cytokeratin staining, the absence of PAS-positive staining, the presence of Congo red-positive material between tumor islands (amyloid-like material) and the absence of mitotic figures. Malignance of salivary gland origin was ruled out by the absence of actin and S-100 expression, and clear-cell odontogenic carcinoma was ruled out by the lack of overt cellular atypia, a well-circumscribed lesion, and the presence of amyloid-like material as well as the very low Ki-67 labeling index. Additionally, a lack of mitotic figures and the generally good circumscription of the lesion are not characteristics of metastatic diseases of any origin.

It should be noted that clear cells may also occur in other epithelial odontogenic leisons such as ameloblastoma,[19] and calcifying odontogenic cyst.[20] It has been demonstrated that the clear cells of the ameloblastoma was clearly of odontogenic epithelial origin.[19] Moreover, it has also been of opinion that the clear cells of the calcifying odontogenic cyst are possibly odontogenic epithelial cells, which have undergone aberrant degeneration.[20]

For CCCEOT, it has been claimed that the clear cells represent a degenerative process,[4,10] whereas another suggestion indicated that the clear tumor cells represent a feature of cytodifferentiation rather than the degenerative phenomenon.[8] In order to obtain some valuable information, we hereby summarize the reported histochemical, immnohistochemical, and electron microscopic findings (including the current case) for the potential origins of clear tumor cells in CCCEOT in Table 1.

As observed from Table 1, in two cases, the clear tumor cells have been proved to be Langerhans cells, as evidenced by the presence of Birbeck's granules using electron microscopy.[9,14] Indeed, some authors have regarded CEOT containing Langerhans cells as non-calcifying CEOT (Pindborg tumor) with Langerhans cells. On the other hand, it has been shown that the clear cells of CCCEOT contain glycogen in four cases by PAS stain[8,12–13,15] and in two cases by electron microscopy.[8,13] An odontogenic epithelial origin has also been demonstrated for the clear tumor cells in three cases by positive immunohistochemical stainings (chiefly cytokeratin) together with negative stainings for PAS and mucicarmine stains[13–14] and the present case, and in one case by electron microscopy.[10] Both PAS and cytokeratin positivity have been simultaneously reported in one case, in which transition between clear cells and CEOT tumor cells was evident throughout the tumor tissues.[13] Taken together, it may be speculated that the clear-cell change might be derived from the

**Table 1 Clinical characteristics of reported cases of the clear-cell variant of central calcifying epithelial odontogenic tumor**

| Case | Reference | Sex (Age/ year) | Maximum dimension/ cm | Location | Clinical presentation | Radiographic finding | Treatment/follow-up | Summary of HC/IHC/EM studies for origins of clear cells |
|---|---|---|---|---|---|---|---|---|
| 1 | 3 | Male (50) | 1.2 | Posterior mandible | Tender mass | Unilocular mixed radiolucency & radiopacity | Enucleation, free of disease 3 years | Not reported |
| 2 | 4 | Female (68) | 3.0 | Posterior mandible, left | Swelling | Unilocular mixed radiolucency & radiopacity | Curettage, recurrence at 4 months | **EM:** Swollen & empty→tumor cell degeneration |
| 3 | 5 | Female (37) | 0.5 | Anterior mandible | None | Unilocular mixed radiolucency & radiopacity | Enucleation, free of disease 13 months | **HC:** PAS (−) |
| 4 | 6 | Male (65) | Not reported | Posterior mandible, right | Swelling, paresthesia | Unilocular mixed radiolucency & radiopacity | Excision, free of disease 22 months | Not reported |
| 5 | 7 | Female (36) | 10 | Anterior & posterior mandible (bilateral) | Loose teeth, swelling | Multilocular mixed radiolucency & radiopacity | Enucleation, free of disease 2 years | Not reported |
| 6 | 8 | Male (36) | 2.5 | Anterior & premolar mandible (right) | Swelling | Unilocular radiolucency | Partial resection, free of disease 2 years | **HC:** PAS (+) **EM:** glycogen granules |
| 7 | 9 | Female (44) | Not reported | Anterior & posterior maxilla | Swelling | Unilocular radiolucency | Partial maxillectomy, follow-up: not reported | **IHC:** CK (−) **EM:** Birbeck's granules (+), S100 (+)→ Langerhans cell |
| 8 | 10 | Male (38) | 2.5 | Anterior mandible | Swelling | Unilocular mixed radiolucency & radiopacity | Resection, free of disease 2 years | **EM:** tonofilament remnant, desmosomes **HC:** PAS (+, initial; -, later stage) →tumor cell degeneration |
| 9 | 11 | Male (58) | 2.0 | Posterior maxilla | Loose teeth | Unilocular radiolucency | Enucleation, free of disease 10 years | **EM**→Langerhans cell |
| 10 | 12 | Female (59) | 3.8 | Posterior mandible, right | Swelling | Unilocular mixed radiolucency & radiopacity | Resection, free of disease 3 years | **HC:** PAS (minimal focal +); mucicarmine (−) |
| 11 | 13 | Female (14) | Not reported | Posterior maxilla, right | Swelling | Unilocular radiolucency; Radiopacity (at recurrence) | Partial resection, recurrence at 13 years | **IHC:** CK 8, 13, 19, filaggrin, anti-ameloblastoma (+)→odontogenic epithelial origin **HC:** PAS (+) **EM:** glycogen granules |
| 12 | 14 | Male (27) | 1.0 | Posterior and premolar mandible | Swelling | Unilocular radiolucency | Excision, free of disease 1 year | **IHC:** CK (+); S-100, actin (−) **HC:** PAS, mucicarmine (−) |
| 13 | 15 | Female (44) | Not reported | Mandibular angle, right | Swelling | Multililocular mixed radiolucency & radiopacity | Enucleation, free of disease 1 year | **HC:** PAS (+)→glycogen granules |
| 14 | 16 | Male (18) | 3.5 | Anterior maxilla, right, extension to maxillary sinus | Swelling | Unilocular mixed radiolucency & radiopacity | Excision, follow-up: not reported | Not reported |
| 15 | Present case | Female (59) | 3.0 | Retromolar and mandibular ramus, left | Swelling | Unilocular radiolucency | Excision, free of disease 2 years | **IHC:** CK (+); S-100, actin (−) **HC:** PAS (+); mucicarmine (−) |

CD, cytokeratin; EM, electron microscopy; HC, histochemistry; IHC, immunohistochemistry; PAS, periodic acid fast stain.

cytokeratin-positive CEOT tumor cells; these tumor cells initially showed a congregation of initially PAS-positive substance, but when the clear-cell phenomenon enhances, the PAS positivity is consistently absent.[10] Consequently, the potential origin and function of the clear tumor cells in CCCEOT would be more complex as compared to other epithelial odontogenic lesions,[19–20] and the clear-cells in CCCEOT may in fact, represent a more diversity of cell origins encompassing Langerhans cells, degenerated cells containing glycogen granules, and cells of overt odontogenic epithelial origin.

Additionally, one may also question whether the presence of clear cells is of clinical relevance. In 1994, Hicks *et al.*[12] suggested that the existence of clear tumor cells in CCCEOT may imply a more aggressive performance. However, other authors considered that too few cases of CCCEOT have been described to date to attain a confirmative conclusion concerning the impact of the clear-cell population on the biologic activity of CCCEOT (ref. 2). Today, the choice of surgical management of the CEOT depends on the site, size, and amount of bone destruction of the lesion. For mandiblular lesions, the suggested surgical approach is enucleation with vigorous curettage; however, for lesions with more advanced bone infiltration, resection of the tumor should be considered.[1–2] The treatment of choice in the current mandibular case is total excision of the tumor. On the other hand,

hemimaxillectomy is suggested as the treatment of choice for lesions of the maxilla, because maxilla tumors could easily intrude on vital structures.[1–2]

Finally, Anavi *et al*.[14] presented a clinical review of CCCEOT in 2003. After almost ten years, as shown in Table 1, we have updated the data of Anavi *et al*.[14] by adding three more cases,[15–16] including the present case. With only three additional cases, it is unsurprising to observe that the main clinical data shown in Table 1 are largely compatible with the report of Anavi *et al*.[14]

## CONCLUSIONS

We report an uncommon case of CCCEOT arising in the mandible, and additionally, a review of pertinent literature as well as discussion of the potential origins of the clear tumor cells have been presented.

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