Peripheral clear cell variant of calcifying epithelial odontogenic tumor devoid of calcification

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Abstract: A clear cell variant of calcifying epithelial odontogenic tumor (CCEOT) affecting an extraosseous site is described. A 60-year-old male patient presented with gingival swelling on the lingual side of the anterior mandible. The results of biopsy suggested clear cell odontogenic carcinoma, and marginal resection of the mandible was performed. The resected specimen was composed of eosinophilic and clear cells with deposits of amyloid-like material. The clear cells exhibited granules that were positive for PAS. There was no calcification in the resected lesion. Based on these features, the conclusive diagnosis was peripheral CCEOT without calcification. No signs of recurrence were evident after 3 years of follow-up.

Keywords: CCEOT; without calcification; peripheral; clear cell; clear cell odontogenic carcinoma.

Introduction
Calcifying epithelial odontogenic tumor (CEOT) was first described as a segmented disease in 1955 by Pindborg. CEOT is rare and accounts for only 1% of all odontogenic tumors (1). Radiography demonstrates unilocular, and more often multilocular radiolucency. However, the density and size of the tumor may vary. The most definitive pathological feature of classic CEOT is the presence of amyloid-like material and Liesegang ring calcification. However, absence of, or minimal, calcification in CEOT is very rare.

Although most cases of CEOT occur at intraosseous sites, a few lesions may also occur at extraosseous or peripheral sites. There have been few reports of peripherally located CEOT.

The clear cell variant of CEOT (CCEOT) was first described in 1967 by Abrams and Howell (2). The occurrence of clear cells in CEOT is rare, and has been reported in approximately 8% of CEOT cases (3). The lesion is characterized by polyhedral epithelial cells alternating with large epithelial cells with a clear, foamy cytoplasm, well-defined borders, considerable variation in nuclear size, and some vacuolated nuclei. Moreover, because clear cells have been described in other lesions of the jaw, differential diagnosis includes peripheral ameloblastoma, clear cell odontogenic carcinoma (CCOC) and metastatic disease originating from kidney carcinoma (4,5).

Here we describe the clinical, radiographic, and microscopic features of a very rare case of extraosseous peripheral CCEOT without calcification in the lower incisor area.

Case Report
A 60-year-old male patient presented at the Department of Oral and Maxillofacial Surgery, Tohoku University Hospital, seeking treatment for painless swellings in the
mandible. The lesion had gradually expanded over the previous 30 years. The patient had smoked 20 cigarettes daily for 30 years, but there was no significant medical history, family history or complicating diseases.

The lesion was located on the lingual side of the lower gingiva extending from the right second premolar to the canine, measured approximately 3.1 cm in diameter, and presented a regular-appearing mucosal surface pattern with elastic hardness (Fig. 1). A panoramic radiograph and computed tomography revealed alveolar bone loss that was consistent with periodontal disease and discrete superficial cupping resorption in the right anterior tooth area (arrow). An incisional biopsy specimen revealed proliferative nests composed of large clear cells and small polygonal cells with eosinophilic cytoplasm lying in a cellular fibrous stroma without calcification. There were clear cells exhibiting periodic acid-Schiff (PAS)-positive granules in the cytoplasm. These histological features were consistent with clear cell odontogenic carcinoma (Fig. 3A, B). There were no metastatic lesions in the cervical lymph nodes or distant organs. Therefore, marginal resection of the mandible, including the neoplastic lesion with a 10-mm safety margin, was performed under general anesthesia. Micro CT of the resected specimen revealed superficial cupping resorption of the alveolar bone on the lingual side (Fig. 4A, B). Histologically, the extirpated specimen showed neoplastic tissue causing elevation of the gingival mucosa and superficial cupping resorption of the alveolar bone on the lingual side of the mandible (Fig. 5).

The neoplastic tissue comprised irregular cords and nests of polyhedral epithelial cells and intercellular amyloid-like materials (Fig. 6A). Calcification could not be detected in any part of the neoplastic tissue. Neoplastic cells exhibiting pleomorphic and hyperchromatic nuclei possessed both eosinophilic and clear vacuolated cytoplasm (Fig. 6B). The clear neoplastic cells exhibited periodic acid-Schiff (PAS)-diastase-positive glycogen granules in the cytoplasm (Fig. 6C). A large amount of intercellular amyloid-like material stained by direct fast scarlet (DFS) was present (Fig. 6D).

The final histopathological diagnosis was the clear cell variant of CEOT, and there was no evidence of disease recurrence after 3 years of follow-up.

Discussion

CCEOT shows some areas of typical polyhedral epithelial cells within the tumor. The nuclei show considerable
variation in size and shape. Deposition of extracellular amyloid-like material and widespread calcifications are typical. Minimal or absent calcification in CEOT is rather exceptional, and only three cases of this type have been reported (6).

Peripheral CCEOT is extremely rare, only 10 cases having been reported up to 2009 (Table 1). The site most commonly affected by the peripheral variant of CCEOT is the anterior region of the mandible (7,8), which was also the location in the present case. The literature suggests that CCEOT is more aggressive with a higher tendency to relapse (9). The surgery employed for the 11 reported patients (including the present one) was complete or partial resection in 3 (27%) and excision in 8 (73%). The duration of follow-up was 1-10 years (mean, 5.7 years) for patients with peripheral lesions (Table 1).

Although initial analysis of the incisional biopsy specimen had yielded a diagnosis of CCOC, a definitive diagnosis of CCEOT was made on the basis of PAS-positive glycogen deposition and DFS-positive stromal materials (7,8). As CCEOT is characterized by amyloid-like material and calcification, DFS staining is done to confirm the former. Congo red staining for amyloid is widely performed, but DFS gives the desired result, and many facilities do this routinely. In comparison with Congo red staining, DFS has a number of advantages:

### Table 1 Clinical characteristics of peripheral CCEOT

| Author                  | Sex/Age (y) | Size (cm) | Location            | Clinical aspect | Treatment       | Follow-up period |
|-------------------------|-------------|-----------|---------------------|-----------------|-----------------|-----------------|
| Abrams and Howell 1967  | F/16        | 0.5       | Anterior mandible   | Swelling        | Excision        | FOD3y           |
| Wertheimer et al. 1977  | M/20        | 1.5       | Maxilla bicuspid    | Swelling        | Excision        | ND              |
| Ai-Ru et al. 1982       | F/32        | ND        | Posterior mandible  | ND              | Partial resection | FOD10y           |
| Ai-Ru et al. 1982       | F/42        | ND        | Mandible bicuspid   | ND              | Resection       | FOD2y           |
| Houston and Fowler 1997 | M/64        | 1.5       | Palate, cusp-bicuspid | Swelling       | Excision        | FOD4y           |
| Houston and Fowler 1997 | M/27        | 1.4       | Posterior mandible  | ND              | Excision        | FOD4y           |
| Orsini et al. 2000      | M/32        | ND        | Anterior mandible   | Swelling        | Excision        | FOD4y           |
| Mesquita et al. 2003    | F/48        | 2.0       | Anterior maxilla    | Mass            | Excision        | FOD2.5y         |
| Oliveira et al. 2009    | F/43        | 2.0       | Anterior maxilla    | Mass            | Excision        | FOD1y           |
| Habibi et al. 2009      | F/70        | 5.2       | Anterior maxilla    | Mass            | Excision        | ND              |
| Present case            | M/60        | 3.1       | Anterior mandible   | Mass            | Marginal resection | FOD3y           |

ND, not described; FOD, free of disease

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**Fig. 5** Gross microscopic features (hematoxylin-eosin, ×10). The tumor tissue had caused elevation of the gingival mucosa and superficial cupping resorption of the alveolar bone on the lingual side of the mandible.

**Fig. 6** Microscopic features. A: Irregular cords and nests of polyhedral epithelial eosinophilic cells and rich intercellular amyloid-like materials (hematoxylin-eosin, ×100). B: Nests and cords of polyhedral eosinophilic cells and clear cells with clear, foamy, and vacuolated cytoplasm (hematoxylin-eosin, ×200). C: Tumor cell lymphocytes composed of clear cells. These clear cells showed a granular positive reaction by PAS (PAS, ×200). D: Amyloid-like materials stained by direct fast scarlet (DFS) (DFS, ×100).
1) co-staining is small; 2) sorting is easy and uneven; 3) when Congo red is used to stain skin amyloid, it is difficult to obtain a strongly positive image. For these reasons, DFS staining is recommended.

Although metastatic disease originating from the kidney may exhibit clear cells, absence of mitotic figures or atypical cells in the present case ruled out metastatic renal cell carcinoma. CCOC is composed of various populations of clear cells within a hyalinized stroma that may be confused with the amyloid-like material found in CEOT (8).

Hicks et al. (10) suggested that the presence of clear cells in CEOT suggests more aggressive behavior. It has been reported that the presence of clear cells in CEOT may indicate increased local tumor aggressiveness and a higher recurrence rate. CCEOT has a more marked tendency for cortical bone perforation than CEOT, ameloblastoma, keratocystic odontogenic tumor, and other benign odontogenic tumors (7,9). Cortical bone perforation is considered to be a sign of aggressiveness, and in slow-growing tumors of the jaw, bone perforation is rare.

In conclusion, it is important to note the presence or absence of clear cells in histopathological examination because CCEOT has a more aggressive impact on neighboring tissues compared with CEOT; however, if adequate treatment is performed, it does not recur often. The presence of clear cells even in small lesions is a strong indicator that extensive excision is required.

Conflict of interest
None declared.

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