Malignant Variant of Calcifying Epithelial Odontogenic Tumor with Neuroendocrine Differentiation

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ABSTRACT

A 60-year-old female presented with asymptomatic failing mandibular dental implants. Computed tomography (CT) showed a partially calcified, hypointense lesion within the soft tissues, measuring 1.3 x 0.8 x 1.0 cm along the buccal cortex. Incisional biopsy demonstrated a basaloid type of tumor composed of sheets of cells with plump ovoid nuclei, distinct nucleoli, and scant eosinophilic cytoplasm. Mitoses were present, averaging about 2 per 10 high power fields with scattered individual apoptotic cells. Numerous laminated calcified bodies (Liesegang rings) were observed with confluence of these bodies to form larger foci of dystrophic mineralization. These features clearly established the malignant nature of this tumor. Immunohistochemically, the tumor was positive for synaptophysin, focally positivity for CAM 5.2 and had a Ki-67 proliferation index of approximately 25%. This is the first report of a tumor with features of a malignant variant of calcifying epithelial odontogenic tumor and neuroendocrine differentiation.

KEYWORDS: calcifying epithelial odontogenic tumor, neuroendocrine, malignant variant, dental implant

CLINICAL PRESENTATION

A 60-year-old female with a past medical history of hypertension, hyperlipidemia, and type II diabetes mellitus was found to have a gingival lesion during dental implant follow-up examination. Her family history was non-contributory. Intraoral examination revealed firm redundant gingival tissue around a failing implant of the right posterior mandible. A clinical diagnosis of granulation tissue was favored with a need to rule out malignancy. Cone-beam computed tomography (CT) of the mandible showed a hypointense lesion with punctate loci of mineralization within the soft tissues measuring 1.3 x 0.8 x 1.0 cm (**Figure 1**). There was deformity and scalloping of the adjacent buccal cortex. The lesion abutted the anterior border of the masseter muscle.

PATHOLOGY FEATURES

Biopsy revealed a tumor consisting of sheets of primitive basaloid type cells with some cells demonstrating scant eosinophilic cytoplasm (**Figure 2**). Many of the tumor cells

Figure 1. Hypointense lesion with punctate loci of mineralization (CT mandible)

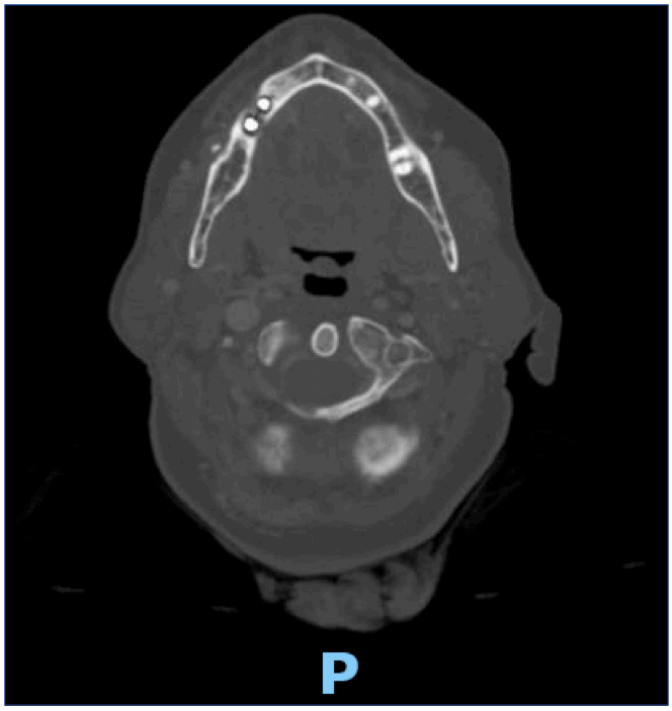
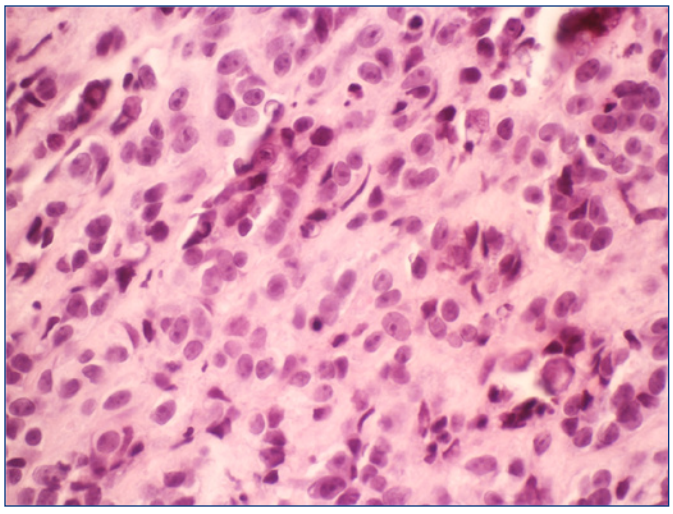


Figure 2. Histological examination of biopsy tissue. Nests and cords of basaloid type cells with some cells demonstrating scant eosinophilic cytoplasm and prominent nucleoli.



had multiple nucleoli. Individual cell necrosis and apoptotic bodies were noted. Mitoses were readily identified and number about 2/10 high power fields (HPF's). Abundant psammomatoid calcifications were noted throughout the tumor.

Tumor cells were positive for synaptophysin and demonstrated focal positivity for CAM 5.2. The Ki-67 proliferation index was approximately 25%. The following immunohistochemical stains were negative: CK7, CK20, AE1.3, S-100, SOX-10, chromogranin, CD56, PAX-8, CA125, CDX2, TTF-1, PR, ER, and WT-1. The tumor was diagnosed as a malignant epithelioid neoplasm, consistent with a high-grade neuroendocrine carcinoma.

Two months after initial biopsy, the patient underwent wide right composite mandibular resection under general anesthesia. The specimen consisted of a 5.1 x 3.3 x 2.0 cm composite resection of the right mandible (**Figure 3**).

Histological examination of the lesion showed cytologic features identical to those seen in the biopsy. A distinctive feature of this tumor (not seen in the biopsy) was the presence of numerous scattered laminated calcified bodies (Liesegang rings); these bodies confluence to form larger foci of dystrophic mineralization (**Figure 4**).

Small nests of the tumor cells were seen to infiltrate underlying cortical bone. In addition, the tumor produced a 0.2 cm intra-lymphatic metastasis immediately adjacent to an otherwise uninvolved lymph node (**Figure 5**). These features clearly established the malignant nature of this tumor.

Additional immunohistochemical examination performed on the resection specimen demonstrated focal positivity for GFAP. Congo red stain for amyloidosis was negative.

Figure 3. Right composite mandibular resection (cross sections)

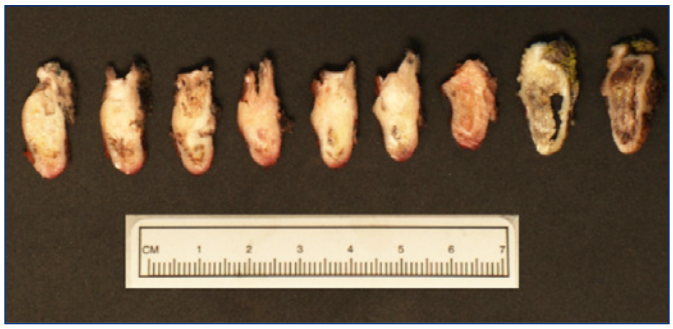


Figure 4. Scattered laminated calcified bodies (Liesegang rings)

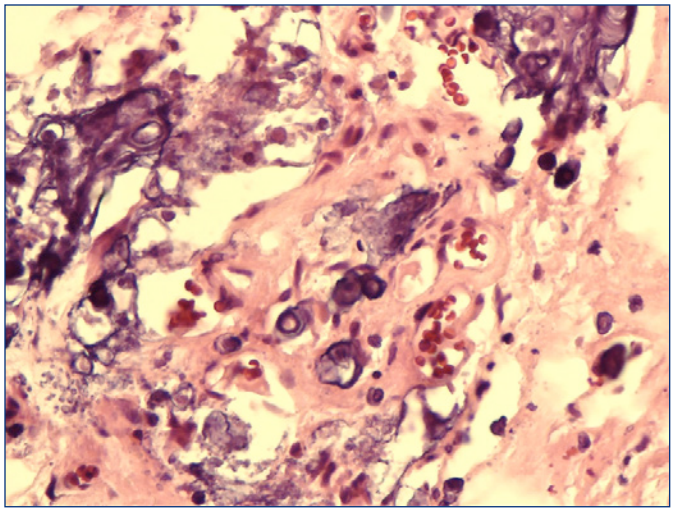
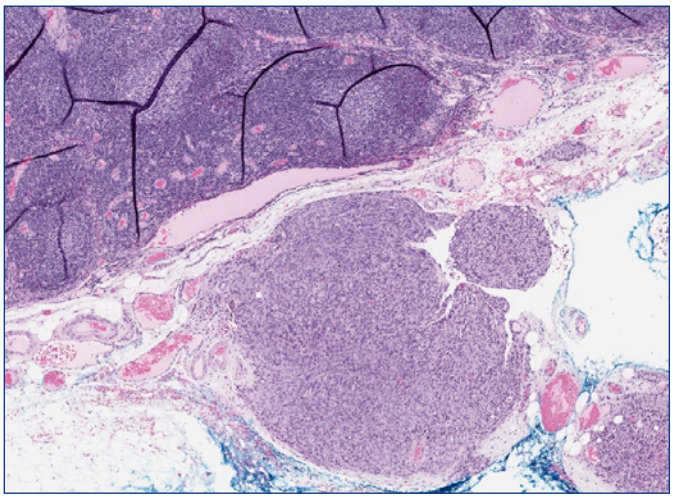


Figure 5. 0.2 cm intra-lymphatic metastasis



DISCUSSION

Calcifying epithelial odontogenic tumor (CEOT) is a rare benign odontogenic tumor first described by Jens Jørgen Pindborg in 1955.[1, 2] Since then, it is often eponymously referred to as "Pindborg tumor". CEOT accounts for <1% of odontogenic tumors,[1] and are most frequently observed in the mandible, with 80% being in the premolar or molar region.[3]

CEOT is composed of nests of polyhedral neoplastic cells, with eosinophilic cytoplasm, nuclear pleomorphism and prominent nucleoli. A distinct feature of this tumor is the presence of stromal amyloid deposition with concentric calcific deposits called Liesigang ring.

A malignant form of this tumor is exceedingly rare, only seven cases have been reported in the literature (**Table 1**).[4] These tumors exhibit nuclear pleomorphism, frequent mitotic figures and vascular invasion, as well as increased proliferative activity assessed by immunostaining for Ki-67.[4] Definitive resection of the lesion with tumor-free surgical margins and long-term follow-up is the recommended therapy.[4]

Several features in this case suggest a diagnosis of malignant variant of CEOT. The pattern of calcification in the form of concentric 'Leisegang rings' closely resembles the calcifications seen in COET.[3,4] The deep submucosal gingival location near cortical bone is consistent with derivation from odontogenic epithelium. Immunohistochemical positive staining for low molecular weight cytokeratin (CAM 5.2) and GFAP are consistent with the diagnosis. The absence of any amyloid-like protein deposition is unusual for a diagnosis of a usual CEOT, while the characteristic

Table 1. Published case reports of malignant calcifying epithelial odontogenic tumors. Drafted in part from Demian et al.[4]

Author	Clinical features	Histology	Location	Publication Year
Demian et al.[4]	Cortical plate perforation, soft tissue extension and distant metastasis (brain)	Nuclear and cellular pleomorphism, mitotically active with necrosis	Mandible	2010
Kawano et al.[5]	Mandibular cortical plate perforation with soft tissue invasion and distant metastasis (lung)	Cellular and nuclear pleomorphism, vascular invasion	Mandible	2007
Kumar et al.[6]	Lingual cortical plate expansion, perforation and distant metastasis (pelvic bone)	Primary: CEOT, Recurrence: Clear cell odontogenic carcinoma	Posterior mandible	2003
Cheng et al.[7]	Perforation of mandibular cortical plates with pathologic fracture	Clear cells, mitotically active, showing pleomorphism and vascular invasion	Anterior mandible	2002
Veness et al.[8]	Perforation of the mandibular cortical plate with soft tissue invasion and nodal metastasis	Recurrence: Mitotically activity with vascular invasion	Mandible	2001
Bouckaert et al.[9]	Intracranial extension with invasion of the orbital floor	Cellular and nuclear pleomorphism	Maxilla	2000
Basu et al.[10]	Perforation of mandibular cortical plate with soft tissue invasion and nodal metastasis	Cellular and nuclear pleomorphism, mitotically active	Mandible	1984

polyhedral epithelial cells with distinct cellular outlines and intercellular bridges preclude a diagnosis of benign CEOT.

Neuroendocrine carcinoma (NEC) constitutes a heterogeneous group of tumors with varying clinical manifestations, histologic appearances, degrees of differentiation, biologic behaviors, and prognoses. Thus far, only a small number of such tumors have been reported in the oral cavity.[11] In this case, the morphologic and immunohistochemical findings were suspicious for NEC. The lesion consisted of small basaloid tumor cells compatible with a small cell neuroendocrine carcinoma. Individual necrotic cells were present. Immunohistochemistry in this case was positive for synaptophysin and the Ki-67 proliferation index was approximately 25%. The atypical location of the lesion, presence of psammomatoid calcifications and the absence of additional neuroendocrine immunohistochemical markers, mitigates against the diagnosis of a typical NEC.

An additional differential was that of a minor salivary gland tumor, although most minor salivary gland tumors occur in the palate.[12] Salivary gland carcinomas displaying exclusively myoepithelial differentiation, known as myoepithelial carcinoma (MYEC), are rare.[13] A malignant minor salivary gland tumor with a predominant myoepithelial cell component was considered in the differential diagnosis of this case. This was, in part, due to sheets of uniform cells with plump, ovoid nuclei and eosinophilic cytoplasm, which can be seen in a MYEC. This tumor was located on the alveolar ridge, a locus devoid of minor salivary gland, excluding a diagnosis of a salivary gland tumor. Additionally, the neoplastic cells failed to demonstrate positive staining for calponin and AE1/AE3 which are positive in 93% and 63% of MYECs respectively.[13]

In summary, the findings in this case most likely represents a malignant COET with neuroendocrine differentiation. This is supported by the morphological findings of scattered laminated calcified bodies (COET) and positivity for synaptophysin.

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Disclosures

Funding: No funding was provided for this manuscript.

Conflict of interest: Author SH is the cofounder of CloudPath Diagnostics LLC, New York.

Acknowledgments: We would like to thank the pathologists at Long Island Jewish Medical Center for their help in working up this case.

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