A Case of Ectopic Odontogenic Ghost Cell Tumor: Histogenetic Features of a New Entity

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Case report

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Abstract

Background: Odontogenic tumors arising from extra-alveolar sites are extremely rare. Dentinogenic ghost cell tumor (DGCT) is an uncommon odontogenic neoplasm characterized by *CTNNB1* mutation, ghost cell appearance, and dentinoid-like calcification. We present a case of an ectopic DGCT arising from a calcifying odontogenic cyst in the floor of the mouth.

Case presentation: A 72-year-old man presented with a painless sublingual swelling. Imaging revealed a multi-lobulated, solid-cyst mass on the floor of the mouth. Cytology showed folded epithelial clusters composed of basaloid cells, keratinized material, and dentinoid matrix. Histology also revealed a multi-cystic, cribriform to solid nest. Immunohistochemically, CK19, CK5/6, bcl-2, and p63 were diffuse positive. *CTNNTB1* mutation was detected, leading to the final diagnosis of an ectopic DGCT. There was no recurrence during a 6-month follow-up.

Conclusion: This is the first report to comprehensively describe the clinicopathological features of an ectopic DGCT of odontogenic origin, developing similarly to that of a true odontogenic DGCT. Accurate diagnosis of this rare entity is necessary to avoid overtreatment.

Background

Odontogenic tumors arising from extra-alveolar sites are extremely rare [1–4]. It remains unclear if such reported lesions were of true odontogenic origin due to the absence of the precursor lesion and/or lack of genetic analysis. Three odontogenic ghost cell tumors of the oral cavity are known: dentinogenic ghost cell tumor (DGCT), calcifying odontogenic cyst (COC), and ghost cell odontogenic carcinoma (GCOC) [1, 2]. DGCT accounts for 0.3–0.5% of all odontogenic tumors and is characterized by dentinoid-like calcification and ameloblastoma-like epithelial islands with ghost cells exhibiting pale, eosinophilic, round, anuclear cytoplasm [1–3]. DGCT arises either de novo or from a preceding COC and involves *CTNNB1* mutation [1–3]. Most DGCTs occur in the jaw (intraosseous DGCT) and rarely in the gingiva or alveolar mucosa (peripheral DGCT). However, two extra-alveolar (ectopic) odontogenic ghost cell tumors or odontogenic-like tumors have also been reported [4, 5].

We present a case of ectopic DGCT arising from a COC on the floor of the mouth. This is the first report of an ectopic DGCT having an odontogenic origin, with a development pathway and precursor lesion similar to that of a true odontogenic DGCT. We believe this report could promote accurate diagnosis of this rare entity.

Case Presentation

A 72-year-old Japanese man with no remarkable medical or family history presented with a painless sublingual swelling discovered during follow-up for myocardial infarction. Clinical examination revealed an elastic mass in the sublingual area covered by normal mucosa. Magnetic resonance imaging (MRI) showed a well-circumscribed lobulated, multi-cystic solid mass located on the floor of the mouth (Fig.

1a). There was no connection between the mass and the gingiva and jaw bone (Fig. 1b). Fine needle aspiration showed folded epithelial clusters with duct-like formation (Fig. 2a). These clusters consisted of basaloid cells lacking prominent nuclear atypia and admixed orange G positive, round material lacking nuclei. Peripheral palisading and some hyalinized dentin-like contents were observed (Fig. 2b, c). Cytologically, a basaloid tumor was suspected, and a diagnosis of “atypia of undetermined significance” was considered. Based on the location and cytological features, a sublingual tumor was suspected, and tumor excision was performed. Intraoperative findings revealed a circumscribed mass with no connection to the alveolar bone and oral floor mucosa.

The surgical specimen was a tan-white, elastic, lobulated solid mass, including multi-small cystic spaces (Fig. 3a). Histological examination revealed a multi-cystic, solid mass surrounded by a thin fibrous capsule. The cyst lining, of variable thickness, was composed of squamous-to-polygonal epithelial cells, which translated to the plexiform and cribriform component adjacent to the dentinoid material deposition (Fig. 3b-d). Both the cyst and solid components had anuclear eosinophilic cells (Fig. 3e). The tumor nest contained basaloid cell proliferation with peripheral palisading (Fig. 3e). Tumor cells showed hyperchromatic nuclei with mild atypia and mitoses (2/10HPF). There was no invasion of the adjacent salivary gland, adipose tissue, lymphovascular, or perineural structures. In the gland-like structure, alcian blue staining showed focal positivity, whereas d-PAS was negative. Immunohistochemically, CK19, CK5/6, bcl-2, and p63 were diffusely positive. Nuclear accumulation of β -catenin was detected (Fig. 3f) and Ki-67 index was 5%. Myoepithelial cell markers, such as S-100, GCDFP, and WT1, were absent. Immunostaining for ductal markers, such as CK7, was positive in the cyst wall, whereas that for CEA was negative. There were no true ducts composed of ductal cells and myoepithelial or basaloid cells. Next-generation sequencing (AmpliSeq Cancer Hotspot Panel V2) revealed missense point mutation in *CTNNB1* (p.Ile35Ser, c.104T > G). A final diagnosis of DGCT associated with COC on the floor of the mouth was established. The resection margin was tumor-free, and no additional treatment was performed postoperatively. The patient was followed up for 6 months with no sign of recurrence on MRI.

Discussion And Conclusion

Odontogenic ghost cell lesions, originally described by Gorlin et al. in 1962 [3], comprise COC, DGCT and GCOC [1, 2]. DGCT is considered the solid counterpart of COC and is occasionally associated with it. These lesions can be classified as central (intraosseous) or peripheral (gingival or alveolar mucosal) based on their clinical presentation, and an extraoral or ectopic DGCT is not yet an established entity [1, 2].

Clinically, most DGCTs occur in the jaw bone (maxilla:mandible = 1:1) and show benign but locally infiltrating behavior [1, 2]. They are more common in men (M:F = 2:1), especially at a younger age (range 11–79 years, mean: 39.7) [1]. The patients usually complain of progressive or slow-growing nodules with swelling, with or without pain [1, 6]. Radiologically, DGCT shows a cystic or solid mass with calcification [7]. In the present case, although the patient was older than the mean age for DGCT occurrence, the imaging findings were consistent with those reported previously [1, 2, 7].

To our knowledge, this the first report to meticulously describe the cytological findings of DGCT. The cell cluster chiefly consisted of basaloid cell proliferation with peripheral palisading. These findings are consistent with those of basal cell adenoma/carcinoma, and we also suspected salivary gland tumors. However, calcification and admixed orange G positive structures without nuclei, similar to ghost cells, are a differential feature and therefore an important cytological feature of DGCT.

The histological features of DGCT include basaloid cell proliferation with ameloblastoma-like epithelial nests resembling the stellate reticulum. Aberrant keratinization was seen with ghost cells having enlarged, polygonal eosinophilic cytoplasm, with or without nuclei, and immature to mature dentinoid or dentino-osteoid structures [1, 2]. Findings indicating the odontogenic nature of the tumor and its transition from a COC are important. The neoplastic cells have been shown to be strongly positive for cytokeratin AE1/3, 5, 7, 14, and 19, but negative for vimentin, desmin, SMA, and CD34. The Ki-67 index has been reported to be < 5% [1, 2]. These histological findings are consistent with those of the present case.

Recently, *CTNNB1* mutations and/or nuclear β -catenin accumulation were detected in the histologically analog groups of basaloid tumors with obligate ghost cell differentiation, such as odontogenic ghost cell lesions including COC, DGCT, and GCOC [8, 9], basal cell adenoma/carcinoma [1, 2], pilomatrixoma, pilomatrical carcinoma [10, 11], and adamantinomatous craniopharyngioma [12]. Phosphorylated CTNNB1 activates WNT signaling and promotes nuclear β -catenin accumulation [8, 13], which elicits differentiation of the tumor cells into hair-like cells called ghost cells [8, 14]. We analyzed the hot spots in 50 genes commonly associated with cancer by target next-generation sequencing, and only *CTNNB1* mutation was detected.

Considering the anatomical site and histogenetic features, the most important differential diagnosis in the present case is of basal cell adenoma/carcinoma. However, basal cell adenoma/carcinoma exhibits two-cell morphology consisting of CK7-positive ductal structures and p63, SMA, CK5/6, WT-1, or podoplanin positive myoepithelial/basal cell components, unlike the findings of the present case. Moreover, all above-mentioned basaloid tumors with ghost cell differentiation lack histological findings of dentinoid material and precursor COC-like cystic components.

To date, only two cases of ectopic dentinogenic ghost cell-like lesions have been reported. One was a DGCT-like lesion in the ethmoid sinus of an 8-year-old boy [4], and the other was a GCOC-like carcinoma on the floor of the mouth of a 54-year-old man [5]. Both exhibited characteristic odontogenic epithelium proliferation with ghost cells but lacked the anatomic association to the oral and alveolar mucosa and bone on radiological, intraoperative, and pathological examinations. Further, *CTNNB1* mutation was detected in the latter case. The clinicopathological features of the present case were similar to those reported previously. Moreover, the characteristic precursor lesion, COC, was detected, with no history of an odontogenic tumor, trauma, or surgery that could have caused tumor dissemination or metastasis.

Based on this clinical, histological, and genetic evidence, a final diagnosis of extraosseous DGCT arising from a COC in the floor of mouth was confirmed.

The development of DGCT occurs through two major pathways: de novo or from a preceding COC. However, the true etiology of an extraosseous DGCT remains unclear [4, 5, 15]. Peripheral DGCT can originate from oral epithelium following trauma or exposure to an irritating agent [6, 15]. In the present case, these factors were absent, and the lesion had no connection with the oral mucosa. Therefore, ectopic odontogenic epithelium may have been associated with the tumor's development.

The recurrence rates of central and peripheral DGCT are 73% and 0%, respectively [1]. While segmental resection is indicated for central DGCT, simple excision is recommended for peripheral DGCT. As an ectopic DGCT is extremely rare, the tumor aggressiveness and optimal treatment are unknown. Liu et al. [4] reported no recurrence of an ectopic DGCT arising from the ethmoid sinus after endoscopic sinus surgery, during a 2-year follow-up. Similar to our findings, they observed that the Ki-67 labeling index was not high, and there was no invasion of the adjacent tissue, vascular, and perineural structures, suggestive of low malignant potential of ectopic DGCT. In our opinion, simple excision of the tumor is therefore justified, and further studies are needed to clarify the nature of the tumor.

This report described a case of DGCT occurring as an ectopic lesion. Despite characteristic histological features, its diagnosis is difficult. Comprehensive clinicopathological examination is important to accurately identify this rare entity to avoid misdiagnosis and overtreatment.

List Of Abbreviations

COC, calcifying odontogenic cyst; DGCT, dentinogenic ghost cell tumor; GCOC, ghost cell odontogenic carcinoma; HE, hematoxylin and eosin; MRI, magnetic resonance imaging

Declarations

Ethics approval and consent to participate

This brief report was conducted in accordance with the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Board of Kansai Medical University Hospital (Approval no.: 160954). Written informed consent was obtained from the patient.

Consent for publication

Written informed consent was obtained from the patient for the publication of this report.

Availability of data and material

Not applicable

Competing interests

The authors declare that they have no competing interests.

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No funding was received for conducting this study.

Authors' contributions

YN, CO, MI, KO, KS, NH, YE, and KT diagnosed the present case. TF, MY, AND HI treated the patient clinically. The first draft of the manuscript was written by YN, and all authors commented on the previous versions of the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1

(a) Magnetic resonance imaging (T1-weighted image) reveals a well-circumscribed lobulated mass on the left side of the floor of the oral mouth (arrowhead). (b) A frontal section (T2-weighted image) shows an expanded mass adjacent to the mandible without connection to the gingival mucosa and jaw bone (arrow).

Figure 2

(a) Fine needle aspiration revealed folded epithelial clusters, including duct-like formation (arrows; Papanicolaou stain). (b) Clusters consisting of basaloid cells with admixed orange G positive round material lacking nuclei (arrows) and peripheral palisading (arrowhead; Papanicolaou stain). (c) Hyalinized dentin-like material (Papanicolaou stain).

Figure 3

(a) The surgical specimen was a tan-white, lobulated solid cystic mass. (b, c) The cystic space was lined by thick wall contained polygonal epithelial cells and translated the cribriform or plexiform basaloid component (asterisk, cystic space; hematoxylin and eosin [HE] staining). (d) Dentinoid material (HE staining). (e) The tumor nest with satellite reticulum like cells, including ghost cells and peripheral palisading. (HE staining). (f) Nuclear accumulation of β -catenin (arrows, cystic component; arrowhead, solid component).