



REVIEW ARTICLE

Non-calcifying and Langerhans cell-rich variant of calcifying epithelial odontogenic tumor



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Received 12 February 2016

Available online 28 March 2016

KEYWORDS

calcifying epithelial
odontogenic tumor;
histogenesis;
Langerhans cell;
noncalcifying variant;
prognosis

Abstract This study reported the clinicopathological features, treatment and prognosis of nine cases of noncalcifying and Langerhans cell (LC)-rich calcifying epithelial odontogenic tumor (CEOT) collected from the English literature. Of the nine cases, seven were intraosseous and two were extraosseous. All nine tumors were found in Asian patients. The age of the nine patients ranged from 20 years to 58 years with a mean age of 41 years. There were five female and four male patients. The seven intraosseous cases included six in the anterior and premolar region of the maxilla and one in the posterior region and ascending ramus of the mandible. The two extraosseous cases were located at the upper lateral incisor and premolar gingivae, respectively. Of the seven intraosseous cases, five showed unilocular and two multilocular radiolucency without foci of calcification. Six of the seven intraosseous cases showed resorption of the tooth roots in the tumor-involved region. Histologically, noncalcifying and LC-rich CEOTs were composed of small nests and thin strands of tumor epithelial cells with a relatively high number of LCs among them. This was the reason why we classed these nine cases as

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noncalcifying and LC-rich CEOTs. Two extraosseous cases received total excision of the gingival mass. For the seven intraosseous cases, four accepted partial maxillectomy or mandibulectomy, two received total excision or enucleation, and one underwent curettage. The six cases with the follow-up information available showed no tumor recurrence after a follow-up period of 6 months to 10 years.

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Introduction

Calcifying epithelial odontogenic tumor (CEOT) is a rare, benign, locally-invasive, and slow-growing odontogenic neoplasm which accounts for 1–2% of all odontogenic tumors.¹ It was firstly reported by Pindborg² in 1955 and thus it has also been known as Pindborg tumor for ~50 years. CEOT can be divided into either intraosseous (central, 94%) or extraosseous (peripheral, 6%) type.¹ The intraosseous type appears radiographically as a unilocular or multilocular radiolucent lesion containing calcified structures of varying size and density. Intraosseous CEOT occurs more frequently in the mandible (especially in the premolar/molar region of the mandible) than in the maxilla. Approximately 60% of intraosseous CEOT are associated with an unerupted tooth (or odontoma). The extraosseous type appears as a painless, firm, and sessile gingival mass and it may cause the depression or erosion of the underlying bone.¹

Histologically, the conventional CEOT is composed of sheets, islands, or strands of polyhedral and eosinophilic epithelial cells, large areas or globules of homogeneous and eosinophilic amyloid-like substance, and multiple concentric Liesegang ring calcifications in a fibrous stroma. The tumor epithelial cells may show cellular and nuclear pleomorphism and giant cell formation. However, no increased mitotic figures are found. Based on various histological features, the histological variants of CEOT include CEOT with cementum-like components, clear-cell CEOT, Langerhans cell (LC)-containing CEOT, CEOT combined with adenomatoid odontogenic tumor, and CEOT with myoepithelial cells.¹

The conventional CEOT has more or less foci of calcification. Another variant of CEOT that does not contain structures of calcification within the tumor is reported to be noncalcifying variant of CEOT with LCs.^{3–9} Although the tumor nests of conventional CEOT may occasionally contain LCs, the LC to tumor epithelial cell ratio is ~ 0.8–1.7:100. However, the tumor epithelial nests of noncalcifying variant of CEOT with LCs often contain abundant LCs with the LC to tumor epithelial cell ratio being 42–83:100.⁸ Therefore, we classed this specific type of noncalcifying variant of CEOT with LCs as noncalcifying and LC-rich variant of CEOT. In this study, nine cases of noncalcifying and LC-rich variant of CEOT were collected from the English literature.^{3–9} The clinical, radiographic, and histological features as well as treatment and prognosis of these nine cases of noncalcifying and LC-rich CEOT were analyzed and described in this study.

Materials and methods

Well-documented case reports of noncalcifying and LC-rich CEOT published between 1990 and 2015 were collected from English literature using Medline and from cross-references. The search was made using the keywords “calcifying epithelial odontogenic tumor”, “noncalcifying variant” and “Langerhans cell”. In total, nine accepted cases retrieved from seven articles were selected.^{3–9} The LC-containing conventional CEOT were excluded from the study samples. Data on age, gender, duration, location, symptoms and signs, radiographic features, resorption of tooth roots, histological findings, treatment modalities, and follow-up information were obtained from the original articles, analyzed, and reported.

Results

Clinical features

The demographic and clinical data of nine cases of noncalcifying and LC-rich variants of CEOT are shown in [Table 1](#). All nine noncalcifying and LC-rich CEOTs occurred in Asian patients. The ages of the nine patients at the time of diagnosis ranged from 20 years to 58 years with a mean of 41 ± 13 years. The seven patients with intraosseous noncalcifying and LC-rich CEOT had a higher mean age (45 ± 12 years) than that (30 ± 13 years) of the two patients with extraosseous noncalcifying and LC-rich CEOT. There were five female patients (including two with extraosseous type) and four male patients. The duration of the lesion (from the onset of the lesion to the time of diagnosis) was not stated in two cases. The duration of the resting seven tumors varied from 1 month to several years.

Of the nine cases of noncalcifying and LC-rich CEOT, seven were intraosseous and two were extraosseous. The seven intraosseous cases included six in the anterior and premolar region of the maxilla and one in the posterior region and ascending ramus of the mandible. The two extraosseous cases included one on the left upper premolar gingiva and the other on the labial gingiva of the right upper lateral incisor ([Table 1](#)). Thus, the anterior and premolar area of the maxilla was the most common location (8/9, 88.9%) for the noncalcifying and LC-rich CEOTs. For the symptoms and signs of the tumor, the two extraosseous cases had no symptoms and signs except a gingival swelling. Of the seven intraosseous cases, two had no symptoms, two had both pain and loose teeth, two had loose teeth only,

Table 1 Demographic and clinical data of nine cases of noncalcifying and Langerhans cell-rich variant of calcifying epithelial odontogenic tumor.

Case no.	Author	Age	Sex	Duration (mo)	Location	Symptoms/signs	Radiographic feature	Tooth root resorption	Treatment/follow-up
1	Asano et al 1990 ³	44	F	Several years	#16 to #11 area	No symptom/swelling	Unilocular radiolucency	#11 to #13	Partial maxillectomy/no information
2	Takata et al 1993 ⁴	58	M	6	#23 to #25 area	Loose teeth/no swelling, loss of alveolar bone	Unilocular radiolucency	#23 and #25	Enucleation/10 y without recurrence
3	Wang et al 2006 ⁵	38	M	Not stated	#44 to ascending ramus	Pain/swelling	Multilocular radiolucency	Not stated	Partial mandibulectomy/2.5 y without recurrence
4	Wang et al 2006 ⁵	39	F	24	Left upper premolar gingiva	No symptom/gingival swelling	No change	None	Resection/2 y without recurrence
5	Wang et al 2007 ⁶	52	F	Not stated	#11 to #13 area	No symptom/depression of anterior hard palate	Unilocular radiolucency	#12 and #13	Partial maxillectomy, #16 to #23/no information
6	Afroz et al 2013 ⁷	20	F	12	Labial gingiva of #12	No symptom/gingival swelling	Nonossifying soft tissue mass	None	Total excision/6 mo without recurrence
7	Chen et al 2014 ⁸	40	F	48	#12 to #25 area	Pain and loose teeth/depression of anterior maxilla	Unilocular radiolucency	#21 and #22	Curettage/5 y without recurrence
8	Chen et al 2014 ⁸	58	M	3	#16 to #23 area	Loose teeth /swelling	Multilocular radiolucency	#13 and #16	Partial maxillectomy/10 y without recurrence
9	Tseng et al 2015 ⁹	24	M	1	#23 to #25 area	Biting pain and loose teeth/no swelling	Unilocular radiolucency	#23 to #25	Total excision and tooth extraction/no information

F = female; M = male.

and one had pain only. For the signs of seven intraosseous cases, three had bone swelling, three had depression of the bone, and one had no swelling.

Radiographic features

Regarding the radiographic features, the two extraosseous cases did not cause significant change of the underlying jaw bone. Of the seven intraosseous cases, five showed unilocular radiolucency and the other two exhibited multilocular radiolucency. None of the nine cases showed foci of calcification in the tumor. Six of the seven intraosseous cases showed resorption of the tooth roots in the tumor-involved region. The remaining one intraosseous case did not mention whether it caused tooth root resorption or not.

Treatment and follow-up

For the treatment of the nine cases, two extraosseous cases received total excision of the gingival mass. For the other seven intraosseous cases, four accepted partial maxillectomy or mandibulectomy, two received total excision or enucleation, and one underwent curettage. Three cases did not provide the follow-up information, the other six cases revealed no tumor recurrence after a follow-up period of 6 months to 10 years (mean, 5 ± 4 years).

Histopathological features

Histopathologic features of nine noncalcifying and LC-rich variant of CEOT are shown in Table 2. None of these nine cases showed foci of calcification. LCs were commonly detected in the small nests or thin strands of tumor epithelial cells by anti-CD1a, anti-S-100, and anti-Langerin immunostains. Other LC biomarkers used for recognition of LC included lysozyme, CD43, HLA-DR, and CD68. Areas and globules of amyloid-like substance could be identified by Congo red, thioflavin T, crystal violet, and methyl violet stains. The Congo red positively-stained orange–red areas showed green birefringence when subjected to polarized light. The thioflavin T positively-stained areas exhibited yellow fluorescence under fluorescent microscope. Moreover, amyloid areas were stained metachromatically by crystal violet and methyl violet. The tumor odontogenic epithelial cells usually formed small nests and thin strands that were positive for keratin and AE1 plus AE3. Mild to moderate inflammatory cell infiltrate in the fibrous stroma was present in five cases. Clear cells could be found in the tumor epithelial nests in six cases. In two cases, most of the clear cells except the LC-typed clear cells showed positive reaction with Periodic acid–Schiff stain. In four cases, the tumor epithelial cells and LCs were studied by electron microscopy. Ultrastructurally, the tumor odontogenic epithelial cells showed tonofilament bundles in the cytoplasm and well-developed desmosomes that joined the two

Table 2 Histopathologic features of nine noncalcifying and Langerhans cell (LC)-rich variant of calcifying epithelial odontogenic tumor.

Case no.	Calcification	LC/LC antigens recognized by antibodies	Amyloid/stain used for identifying amyloid	Odontogenic epithelium/epithelial antigens recognized by antibodies	Inflammatory cell	Clear cell/PAS stain	Electron microscopy/LC
1	None	+/S-100 protein, CD1a, lysozyme, CD43, and HLA-DR	+/Congo red, crystal violet, methyl violet, thioflavin T	Small nests and cords/keratin filament	+	+/not done	+/+ with Birbeck granules
2	None	+/S-100 protein	+/Congo red and thioflavin T	Small nests or strands/keratins	–	–/not done	+/+ with Birbeck granules
3	None	+/CD1a, S-100 protein, HLA-DR and CD68	+/Congo red	Small nests and cords/none	+	+/+ and some LC –	+/+ with Birbeck granules
4	None	+/CD1a, S-100 protein, HLA-DR and CD68	+/Congo red	Small nests and cords/none	+	+/+ and some LC –	+/+ with Birbeck granules
5	None	+/CD1a	+/Congo red	Small nests or strands/AE1 + AE3	–	–/not done	Not done
6	None	+/S-100 protein	+/not done	Small nests or islands/AE1 + AE3	–	+/not done	Not done
7	None	+/CD1a, S-100 protein and langerin	+/Congo red	Small nests and cords/none	+	+/not done	Not done
8	None	+/CD1a, S-100 protein and langerin	+/Congo red	Small nests and cords/none	+	+/not done	Not done
9	None	+/CD1a and S-100 protein	+ but scant/Congo red	Small nests and strands/none	–	–/not done	Not done

LC = Langerhans cell.

adjacent tumor epithelial cell surfaces together. The LC revealed an indented nucleus and a few rod-shaped or racket-shaped Birbeck granules but no tonofilaments in the cytoplasm.

Discussion

When the noncalcifying and LC-rich CEOTs were compared with the conventional CEOTs, several characteristic features were noted. The noncalcifying and LC-rich CEOTs occurred only in Asian patients, had a predilection for the anterior and premolar region of the maxilla, had none of calcification foci in the tumor, contained small nests (or islands) and thin strands (or cords) of tumor odontogenic epithelial cells without marked cellular and nuclear pleomorphism, and showed a great number of LCs in the small tumor epithelial nests.³⁻⁹ However, the conventional CEOTs usually occurred in the posterior region of the jaw bone (especially the posterior region of the mandible), were often associated with an impacted tooth or an odontoma (~60%), showed more or less calcified structures with some forming the Liesegang ring calcifications in the tumor stroma, contained sheets or relatively-large islands of polyhedral tumor odontogenic epithelial cells with prominent intercellular bridges, cellular and nuclear pleomorphism, and giant cell formation, and exhibited none or a very small number of LCs in the tumor epithelial nests.^{1,8,10,11}

LCs are bone marrow-derived cells that migrate into the oral epithelium and serve as antigen-presenting cells. As both oral and odontogenic epithelia originate from the same oral ectoderm, it is possible that LCs may also migrate into tumor odontogenic epithelial nests.⁶ In this study, abundant LCs were found in the small tumor epithelial cell nests of noncalcifying and LC-rich CEOT.³⁻⁹ However, few LCs were discovered in sheets and large tumor epithelial cell nests of conventional CEOTs.⁸ Previous studies also found LCs in tumor odontogenic epithelial nests of central granular cell odontogenic tumors¹²⁻¹⁴ and odontogenic fibromas¹⁵ as well as in the lining epithelia of a unicystic ameloblastoma,¹⁶ odontogenic cysts including radicular cyst, dentigerous cyst and odontogenic keratocyst,¹⁷ and a sublingual dermoid cyst.¹⁸ Moreover, LCs can also be detected in tumor epithelia of a skin keratoacanthoma¹⁹ and in lining epithelia of skin epidermoid cysts.²⁰ An interesting finding is that the presence of LCs in the lining epithelia of cysts is highly associated with the inflammation in the underlying or adjacent fibrous cystic wall. For example, the radicular cyst is an odontogenic cyst of inflammatory origin, and thus many LCs are discovered in the hyperplastic lining epithelium of the radicular cyst.¹⁷ Dentigerous cysts and odontogenic keratocysts are developmental odontogenic cysts that are usually not related to inflammation. Thus, very few or no LCs are found in the lining epithelia of dentigerous cysts and odontogenic keratocysts.¹⁷ However, in focal subepithelial fibrous cystic wall with a lymphoplasm cell infiltrate, an increased number of LCs can be detected in the overlying lining epithelia of dentigerous cysts and odontogenic keratocysts.¹⁷ Furthermore, for oral dermoid cyst a significantly higher mean number of LCs can be found in the epithelial lining with a subepithelial chronic inflammatory cell

infiltrate than in that without a subepithelial chronic inflammatory cell infiltrate.¹⁸ In addition, we also demonstrated a greater number of LCs in the lining epithelium of a ruptured epidermoid cyst with inflammation than in the lining epithelium of an intact epidermoid cyst without inflammation.²⁰ In this series of nine cases of noncalcifying and LC-rich CEOT, a mild to moderate lymphoplasm cell infiltrate was found in the focal stroma area in five cases. This may partially explain why there is an increased number of LCs in tumor odontogenic epithelial nests of these five cases of noncalcifying and LC-rich CEOT with inflammation. In addition, small or large globular masses of amyloid were detected either within epithelial cells or within the connective tissue stroma. As the amyloid material is antigenic, we suggest that it may stimulate the migration of LCs from the adjacent blood stream into the tumor odontogenic epithelial nests. In conventional CEOT, the globular masses of amyloid are partially or completely mineralized, and this renders the amyloid materials to lose their antigenicity partially or completely, leading in a limited or no migration of LCs into the sheets or nests of tumor odontogenic epithelia in conventional CEOTs. More studies of a large sample size are needed to further elucidate the exact mechanisms that result in a different number of LCs in the tumor odontogenic epithelial nests of these two variants of CEOT.

In this series of nine noncalcifying and LC-rich CEOTs, all investigators used anti-S-100 protein, anti-CD1a (OKT6), or anti-Langerin immunostains to detect the LCs. S-100 protein is a useful marker for melanoma, Schwannoma and neurofibroma, but is also used to identify LC.^{3-5,7-9,21,22} CD1a and Langerin (CD207) are used as specific markers for LC.^{3,5,6,8,9} Langerin is a specific protein localized in the Birbeck granules of LCs. LCs utilize CD1a and Langerin to efficiently present nonpeptide antigens to T cells.²³ Other LC antigens utilized to detect LCs included lysozyme, CD43, HLA-DR, and CD68.^{3,5} CD43 protein is a sialoglycoprotein found on the surface of thymocyte, T lymphocyte, monocyte, granulocyte, and some B lymphocytes.²⁴ HLA-DR is an MHC Class II molecule on the cell surface of the antigen-presenting cell such as LC. CD68 is a lysosomal glycoprotein that is present in various cells of macrophage lineage including monocyte, histiocyte, and LC.²⁵ Actually, immunostains are quick and useful methods to identify LCs. As the LC possesses the specific Birbeck granules in its cytoplasm, electron microscopy is also a specific method used for the detection of LCs.³⁻⁵

Although CEOT is an odontogenic tumor, its histogenesis is still not very clear. A previous study demonstrated that ~60% of intraosseous CEOTs are associated with an unerupted tooth (or odontoma).¹ Moreover, the tumor cells exhibit morphologic characteristics of squamous epithelium with prominent intercellular bridges. Thus, the tumor cells are suggested to originate from the reduced enamel epithelium of the closely related unerupted tooth or odontoma.¹ For intraosseous CEOTs without the association with an unerupted tooth, the tumor cells may derive from remnants of dental lamina in the jaw bones or epithelial rests of Malassez in the periodontal ligament.^{1,8} Regarding the histogenesis of peripheral CEOTs, the tumor cells are thought to be derived from remnants of dental lamina in the gingiva or basal cells of gingival epithelium.^{1,7}

The treatment modalities for CEOTs range from curettage and enucleation to partial resection of jaw bone, hemimandibulectomy, and hemimaxillectomy. For the mandibular CEOTs, enucleation with a margin of macroscopic normal tissue is recommended. CEOTs of the maxilla, however, should be treated more aggressively, because they are usually not well-defined and seem to grow more rapidly than their mandibular counterparts.¹ If inadequately treated, CEOTs are reported to have a recurrence rate of 14%.²⁶ In this series of nine noncalcifying and LC-rich CEOTs, the six cases with available follow-up information showed no tumor recurrence after a follow-up period of 6 months to 10 years (mean, 5 years). To date, only eight well-documented cases of malignant CEOT were reported in the English literature.²⁷

In conclusion, noncalcifying and LC-rich CEOTs are composed of smaller nests and thinner strands of tumor epithelial cells than conventional CEOTs. A relatively higher number of LCs in tumor epithelial nests is found in noncalcifying and LC-rich CEOTs than in conventional CEOTs. All the noncalcifying and LC-rich CEOTs are found in Asian patients, and they have a predilection for the anterior and premolar region of the maxilla and usually show no calcification foci in the tumor. If adequately treated, no evidence of tumor recurrence is found.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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