原文題目(出處)：	Non-calcifying and Langerhans cell-rich variant of calcifying epithelial odontogenic tumor
原文作者姓名：	Hung-Pin Lin et al
通訊作者學校：	Department of Dentistry, School of Dentistry, National Taiwan University, Taiwan.
報告者姓名(組別)：	陳啟翔 Intern A 組
報告日期：	105.08.11

內文：

INTRODUCTION:

1. Calcifying epithelial odontogenic tumor (CEOT, Pindborg tumor): rare, benign, locally-invasive, and slow-growing odontogenic neoplasm which accounts for 1-2% of all odontogenic tumors.
2. CEOT can be divided into either intraosseous (central, 94%) or extraosseous (peripheral, 6%) type.
   -- intraosseous type:
   a)radiographically: unilocular or multi-locular radiolucent lesion containing calcified structures of varying size and density.
   b)occurs more frequently in the mandible (especially in the premolar/ molar region) than in the maxilla.
   c)60% associated with an unerupted tooth (or odontoma).
   -- extraosseous type:
   painless, firm, and sessile gingival mass and it may cause the depression or erosion of the underlying bone.
3. Histologically finding:
   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.
4. The tumor epithelial cells may show cellular and nuclear pleomorphism and giant cell formation. (However, no increased mitotic figures are found.)
5. Based on various histological features, the histological variants of CEOT include
   a)CEOT with cementum-like components
   b)clear-cell CEOT
   c)Langerhans cell (LC)-containing CEOT
   d)CEOT combined with adenomatoid odontogenic tumor
   e)CEOT with myoepithelial cells
6. The conventional CEOT has more or less foci of calcification while noncalcifying variant of CEOT with LCs does not contain structures of calcification
7. the LC to tumor epithelial cell ratio is
   -- conventional CEOT: 0.8-1.7:100
   -- noncalcifying variant of CEOT with LCs: 42-83:100.
   >> classed this specific type of noncalcifying variant of CEOT with LCs as noncalcifying and LC-rich variant of CEOT.
8. In this study, nine cases were collected from the English literature.

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:

1. 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.
2. Keywords:“calcifying epithelial odontogenic tumor”, “noncalcifying variant” and “Langerhans cell”.
3. In total, nine accepted cases retrieved from seven articles were selected.
4. The LC-containing conventional CEOT were excluded from the study samples.
5. 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:

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.

A) CLINICAL AND RADIOGRAPHIC FEATURES:

1. CLINICAL:

-- 7 intra-osseous; 2 extra-osseous

-- demographic: Asian patients

-- time of diagnosis: 20～58 years (mean: 41±13 years)

a) intraosseous: 45 ±12 years (higher)

b) extraosseous: 30 ±13 years

-- sex: 5 female (including two with extraosseous type); 4 male

-- duration of the lesion from the onset to the time of diagnosis: 1 month to several years (7 cases)

-- location:

a) intraosseous: 6 in the anterior and premolar region of the maxilla; 1 in the posterior region and ascending ramus of the mandible.

b) extraosseous: 1 on the left upper premolar gingiva;

1 on the labial gingiva of the right upper lateral incisor.

>> Thus, the anterior and premolar area of the maxilla was the most common location (8/9, 88.9%)

-- symptoms and signs:

a) intraosseous:

1） symptoms: 2 had no symptoms; 2 had both pain and loose teeth; 2 had loose teeth only; 1 had pain only.

2) signs: 3 had bone swelling; 3 had depression of the bone;1 had no swelling.

b) extraosseous:
no symptoms and signs except a gingival swelling.

2. RADIOGRAPHIC:
-- all without foci of calcification in the tumor
a) intraosseous:
1) showed radiolucency >> 5 unilocular; 2 multilocular
2) 6 cases showed resorption of the tooth roots in the tumor
b) extraosseous: no change of the underlying jaw bone.

B) TREATMENT AND FOLLOW-UP

1. -- Treatment:
a) intraosseous cases: 4 partial maxillectomy or mandibulectomy; 2 total excision or enucleation; 1 curettage.
b) extraosseous total excision of the gingival mass.
-- Follow up:
3 cases did not provide the follow-up information; 6 cases revealed no tumor recurrence after a follow-up period of 6 months to 10 years (mean 5±4 years)

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.

C) HISTOPATHOLOGICAL FEATURES:

1. -- None 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 detectors included lysozyme, CD43, HLA-DR, and CD68.)
-- the tumor odontogenic epithelial cells usually formed small nests and thin strands that were positive for keratin and AE1 plus AE3.
-- 5 cases showed mild to moderate inflammatory cell infiltration in the fibrous stroma.
-- 6 showed clear cells found in the tumor epithelial nests
-- 2 cases, most of the clear cells except the LC-typed clear cells showed positive reaction with Periodic acid-Schiff stain.
-- in 4 cases, the tumor epithelial cells and LCs were studied by electron

microscopy
>> ultrastructurally:
a)the tumor odontogenic epithelial cells showed tonofilament bundles in the cytoplasm and well-developed desmosomes that joined the two adjacent tumor epithelial cell surfaces together.
b)LC revealed an indented nucleus and a few rod-shaped or racket-shaped Birbeck granules but no tonofilaments in the cytoplasm.

DISCUSSION:

1. Noncalcifying and LC-rich CEOTs v.s. conventional CEOTs:
   A) noncalcifying and LC-rich CEOTs
   -- only in Asian patients,
   -- predilection for the anterior and premolar region of the maxilla, -- 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.
   B) conventional CEOTs
   -- occurred in the posterior region of the jaw bone (especially the posterior region of the mandible)
   -- often associated with an impacted tooth or an odontoma (60%)
   -- with 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
   -- exhibiting none or a very small number of LCs in the tumor epithelial nests
2. -- 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.
   -- previous studies found LCs can be in:
   central granular cell odontogenic tumors; odontogenic fibromas ; unicystic ameloblastoma; odontogenic cysts (radicular cyst, dentigerous cyst and odontogenic keratocyst, sublingual dermoid cyst); skin keratoacanthoma; skin epidermoid cysts.
   -- 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
   1) ex: the radicular cyst is an odontogenic cyst of inflammatory origin, and thus many LCs are discovered. 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 dentigerous cysts and odontogenic keratocysts.
   (However, in focal subepithelial fibrous cystic wall with a lymphoplama cell infiltrate, an increased number of LCs can be detected in dentigerous cysts and odontogenic keratocysts.)
   2) LCs number:
   ruptured epidermoid cyst with inflammation > intact epidermoid cyst without inflammation.

-- in this series of nine cases of noncalcifying and LC-rich CEOT, a mild to moderate lymphoplasma 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.
-- Amyloid was detected. 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, amyloid is 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 tumor epithelia in conventional CEOTs.

3. 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 pro- tein is a useful marker for melanoma, Schwannoma and neurofibroma, but is also used to identify LC. CD1a and Langerin (CD207) are used as specific markers for LC.3 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. Other LC antigens utilized to detect LCs included lysozyme, CD43, HLA-DR, and CD68. CD43 protein is a sialoglycoprotein found on the surface of thymocyte, T lymphocyte, monocyte, granulocyte, and some B lymphocytes. 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. 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.
4. Although CEOT is an odtontogenic 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)
   -- the tumor cells 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. 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. 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
5. 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 macro- scopic 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%. 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
6. In conclusion, noncalcifying and LC-rich CEOTs

--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 non- calcifying 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.

題號	題目
1	Which of the following statements about Pindborg tumor is correct? (A) More common in the posterior part of the mandible (B) It is most often encountered in patients over 50 years-old of ages (C) The prognosis of Pindborg tumor is poor (D) male is more than female
答案 (A)	出處：Oral & Maxillofacial Pathology, second edition
題號	題目
2	下列有關 ameloblastoma 及 Pindborg tumor 的敘述，何者正確？ (A) 在放射線影像上，兩者都表現出放射線透射及不透射區 (B) 兩者都是惡性腫瘤，必須大範圍的手術切除 (C) 假如單純的以 enucleation 來治療，兩者的再發率都高 (D) 兩者通常都會包含一顆埋伏齒
答案 (C)	出處：《99 年第一次專門職業及技術人員高等考試~牙醫師(一)-牙醫學(二)》