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Non-calcifying Langerhans Cell-Rich Variant of Calcifying Epithelial Odontogenic Tumor: Systematic review of a Distinct Entity

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Abstract

This article aimed to collectively present the demographic, clinical, radiographic and histopathological features as well as the treatment performed along with its outcome for all the cases of non-calcifying Langerhans cell rich variant of calcifying epithelial odontogenic tumor reported in scientific literature till date. Calcifying epithelial odontogenic tumor (CEOT) is a rare type of odontogenic tumor. The most characteristic feature of the classical CEOT is the presence of amyloid globules and Liesegang ring calcification in the tumor tissue. Here, we present a non-calcifying variant of intraosseous CEOT with the presence of Langerhans cells within tumor epithelial nests. Compared to a typical CEOT, the tumor islands of these cases were thin and composed of a small number of polyhedral epithelial cells. Almost no calcification of homogenous eosinophillic materials was observed. In addition, clear cells which structurally corresponded to Langerhans cell were intermingled in the epithelial islands. Although the Langerhans cell variant of CEOT is a rare entity and behaves similarly to the conventional type, it could show unique clinical and histologic features that may pose problems for differential diagnosis. Prompt recognition of this variant can guide surgical management and alert the clinician to the need for extended follow-up.

Keywords: Langerhans Cells, Calcification, CEOT

Introduction

Calcifying epithelial odontogenic tumor (CEOT) is a rare odontogenic tumor that accounts for approximately 1% of all odontogenic tumors. It is a benign, slow-growing, locally invasive odontogenic tumor(1). It generally

occurs in patients between 20-60 years of age, with a mean age of diagnosis of 40. It affects men and women equally. CEOT can be divided into either intraosseous (central, 94%) or extra osseous (peripheral, 6%) type. 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 unerupted tooth (or odontoma). The extra osseous type appears as a painless, firm, and sessile gingival mass and it may cause the depression or erosion of the underlying bone (2).

Histologically, CEOT consists of three distinct histological components: sheets of polyhedral epithelial cells, amyloid deposits, and calcifications. The most distinctive microscopic feature of classical CEOT is the presence of amyloid globules and Liesegang ring calcifications in the tumor tissue which makes the diagnosis easy. (3).

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 (2)

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 no calcifying variant of CEOT with LCs. Although the tumor nests of conventional CEOT may occasionally contain LCs, the LC to tumor epithelial cell ratio is 0.8 to 1.7 :100. However, the tumor epithelial nests of no calcifying variant of CEOT with LCs often contain abundant LCs with the LC to tumor epithelial cell ratio being 42.1 to 82.7 :100 However, CEOT can show extensive clear-cell change which can make the diagnosis difficult(4).

The present systematic review aimed to collectively present the demographic details, clinical features, histopathological patterns, treatment performed and the outcomes of the cases of Non calcifying Langerhans cell rich CEOT (NCL-CEOT) found in the literature in English. Another objective was to improve the understanding of the lesions with respect to their clinical characteristics, varied histopathological morphology and prognosis. This systematic review has been registered in the International prospective register of systematic reviews–PROSPERO (https: // www.crd.york.ac.uk /PROSPERO/record.php Record Id -CRD42023444626)

Methods

Case reports and case series of NCL-CEOT were retrieved by a systematic search of scientific databases, including Ovid (Walter Kluwer, New York, USA), Medline (National Library of Medicine, Maryland, USA), PubMed Central (National Library of Medicine), Web of Science Citation Index Expanded (Clarivate Analytics, London, UK) and Google Scholar (Google, Mountain View, USA) with the keywords ‘Langerhans cell’ OR ‘Non-Calcifying’ AND ‘CEOT’. Retrieved literature was scanned to identify any cases reported with a name differing from Non calcifying Langerhans cell rich CEOT. Additionally, case reports and case series of NCL- CEOT were also scanned from cross-references. Histopathologically diagnosed cases of NCL-CEOT available in English literature were included in this review. However, lesions with uncertain diagnostic criteria, unclear histopathological characteristics and the

absence of features of non calcifying Langerhans cell rich were excluded from the review.

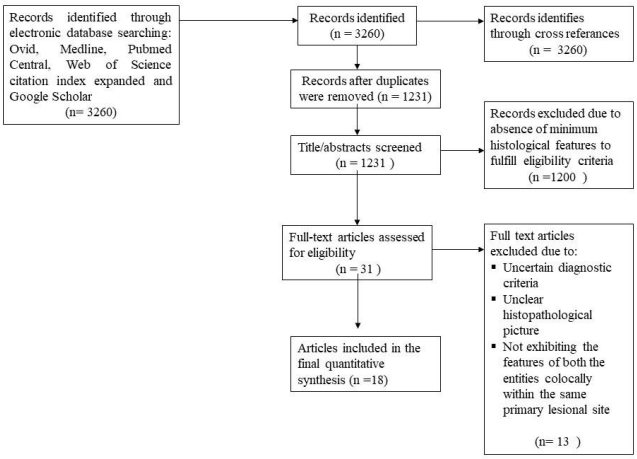

Figure 1: PRISMA flow chart indicating selection process of articles for final qualitative synthesis in the present systematic review.

Criteria for selection and exclusion

Selection criteria included publications written in any of the official European languages reporting cases of CEOTs with Langerhans cells. The studies needed to have enough clinical, radiological and histological information to confirm a definite diagnosis of CEOT. The definitions and criteria of the World Health Classification of Tumors–Head and Neck Tumors book (WHO, 2005), were used to diagnose a lesion as CEOT.

According to World Health Classification of Tumors–Head and Neck Tumors book (WHO,

2022) Calcifying epithelial odontogenic tumor (CEOT) has relatively important changes in that three subtypes have been described as clear cell CEOT, cystic/microcystic CEOT, and non-calcifying/Langerhans cell-rich CEOT.(5)

Although we have used the WHO criteria of 2022 for CEOT diagnosis, reports of studies that did not perform specific staining foramyloid deposition were not excluded. Randomized and controlled clinical trials, cohort studies, case-control studies, cross-sectional studies, case series, and case reports were included.

However, lesions with uncertain diagnostic criteria, unclear histopathological characteristics were excluded from present study

Results

A summary of all cases reported till date is presented in Table 1. Total 13 cases which were satisfying our inclusion exclusion criteria were considered in the review. Out of 13 cases 10 (76.9%) cases were involving anterior maxilla. Whereas 2 (15.4%) were involving posterior mandible and only single case (7.7%) were involving posterior maxilla. Mean age of NCL-CEOT was 77 with 31% cases were in 4^{th} and 5^{th} decade each. (16). In this present review of thirteen NLC-CEOTs, the nine cases with available follow-up information showed no tumor recurrence after a follow-up period of 6 months to 10 years (mean, 5 years) whereas 3 cases were not having any information regarding recurrence.

The basic difference between the classic variant and Non-calcifying Langerhans cell rich variant of CEOT is presented in the table no.2. Differentiating conventional CEOT from the Langerhans cell variant is not difficult. The conventional type affects the premolar and molar region as an asymptomatic slow-growing expansile mass and may feature an unerupted tooth. In contrast, lesions of the Langerhans cell variant have a predisposition for the anterior maxilla and a possibly overlying bone depression. Histopathologically, in the conventional type, the tumour consists of islands and sheets of polyhedral epithelial cells, eosinophilic homogenous amyloid substance, and calcified tissue. In the Langerhans cell variant, very small islands and cords of neoplastic cells with abundant amyloid substance and no calcification are characteristic features.

In conclusion, the Langerhans cell variant of CEOT is rare but consistent. To date, it has only been reported in Asian people, mainly in the anterior portion of the maxilla. This jaw tumour could present features of bone depression with loss of teeth and alveolar bone. The lesion comprises small epithelial islands and amorphous eosinophilic globules of amyloid materials with no apparent calcification. These features are somewhat different from those of conventional CEOT and should alert the pathologists to the differential diagnosis.(3)

Discussion

CEOT is a slowly growing, benign, but locally invasive epithelial odontogenic neoplasm, initially described by Pindborg in 1955. CEOT is predominantly an intraosseous (central) neoplasm but it also occurs as a rare less aggressive peripheral (extra osseous) tumour. It consists of sheets and islands of eosinophilic polyhedral epithelial cells associated with homogeneous pink amyloid deposits that have a tendency for calcification. A clear cell variant has been recognized, which was first reported by Abrams and Howell in 1967. NCL-CEOT is a rare variant of CEOT with less than 30 cases reported in the literature. While it is not surprising to find clear cells in odontogenic lesions, as many are speculated to originate from remnants of the dental lamina which exhibit a reasonable proportion of clear cells, the exact nature of the clear cells in NCL-CEOT has not been elucidated.

In general, clear cells are seen in several different tumours and could result from fixation artifacts, intracytoplasmic accumulation of various substances such as glycogen, mucin, lipid and even scarcity of organelles. It appears that intracytoplasmic glycogen accumulation accounts for the clear nature of the cells observed in most cases of NCL-CEOT. The majority of the clear cells in NCL-CEOT are reported to be PAS positive, possess centrally located round hyperchromatic nuclei and have been shown to be immunoreactive for EMA and cytokeratins.

These findings indicate transformation of the typical polyhedral eosinophilic cells of CEOT to epithelial cells with optically clear cytoplasm through cytoplasmic accumulation and storage of glycogen particles(14).

The presence of LC in CEOT has traditionally been associated with paucity or absence of calcifications. This association which has been described in a few isolated case reports, has culminated in the adoption of the contradictory term ‘‘non-calcifying variant of calcifying epithelialodontogenic tumour with LC’’. LC rich non-calcifying CEOT has further been suggested to be a distinct entity common in the Asian population with a predilection for the anterior maxillary region (6–8)

In 1990, Asano et al. Described a variant of CEO with LC. The case was reported to be unusual inthat no calcifications were identifiable in the histological sections examined. Moreover, in addition to the polyhedral eosinophilic cells, a population of clear cells was observed. The clear cells were negative for glycogen particles when stained with PAS and were immunoreactive for S100protein. Ultra structurally they lacked desmosomes and to no filaments and showed cytoplasmic Birbek granules. The clear cells were interpreted to be LC.(6)

Takata et al reported a case with small epithelial islands and minimal calcification in the homogeneous eosinophilic material. They speculated that the presence of Langerhans cells in tumor nests may play an important role in antigen presentation or regression of CEOT, citing the correlation between number of Langerhans cells and prognosis of gastric cancer(7,15)

Wang et al also found similar finding in further three cases .Anti-CD1a immuno staining also confirmed the

presence of Langerhans cells in odontogenicepithelial nests in our case. The pathologic significance of the presence of Langerhans cells in CEOT is still unclear. Langerhans cells are bone marrow-derived cells that migrate into the oral epithelium and serve as antigen-presenting cells. Because both oral and odontogenicepithelia originate from the same oral ectoderm, it is possible that Langerhans cells may also migrate into tumor odontogenic epithelial nests. These Langerhanscells are very close to the amyloid globules. Therefore, they may phagocytize and process the amyloid material and then present the processed antigens to T lymphocytes in the regional lymph nodes. Owing to the paucity of this special variant of CEOT, the true pathologic significance of the presence of Langerhans cells in CEOT needs further study.(8, 9)

Chen et al reviewed eight cases of CEOT including 2 cases of Langerhans cell variant clinicopathologically and they also reviewed English language literature. Langerhans cells were detected in 2 cases of conventional CEOT and in 2 cases of Langerhans cell variant by immunohistochemistry. They concluded that ,Although the Langerhans cell variant of CEOT is a rare entity and behaves similarly to the conventional type, it could show unique clinical and histologic features that may pose problems for differential diagnosis.(4)

According to Lin et al., the presence of amyloid stimulates LC migration from bloodstream to odontogenic epithelial nests due to antigenicity of amyloid. However, in conventional CEOT, calcifications in amyloid restrict the migration of LCs as mineralization in amyloid leads to a decrease or loss of its antigenicity. Thus, the presence of clear cells and absence of calcification can also be related to the presence of LCs in odontogenic nests of CEOT(3).

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. If inadequately treated, CEOTs are reported to have a recurrence rate of 14%(16). In this present review of thirteen NLC-CEOTs, the nine cases with available follow-up information showed no tumor recurrence after a follow-up period of 6 months to 10 years (mean, 5 years).

Conclusion

Taken together, we suggest that then on-calcifying, Langerhans cell-rich variant of CEOT may have a distinct predilection for occurrence in the anterior and premolar region of the maxilla in contrast to the classical CEOTs that usually occur in the molar and ascending ramus area of the mandible. From the present evidences presence of Langerhans cell can be correlated with absence of calcification and improvement in prognosis of CEOT. More accumulative data are needed to further confirm this specific finding.

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Legend Tables

Sn.	Author	Age	Sex	Duration	Site	C/F	R/F	Treatment	Follow up
1	Asano et al 1990(6)	44	F	Several years	#16 to #11 area	No symptom/swelling	Unilocular Radiolucency	Partial maxillectomy	No Information
2	Takata et al 1993(7)	58	M	6(mo.)	#23 to #25 area	Loose teeth/no swelling, loss of Alveolar bone	Unilocular Radiolucency	Enucleation	10 y without Recurrence
3	Wang et al 2006(8)	38	M	Not stated	#44 to Ascending ramus	Pain/swelling	Multilocular Radiolucency	Partial mandibulectomy	2.5 y Without recurrence
4	Wang et al 2006(8)	39	F	24	Left upper Premolar gingiva	No symptom/gingival swelling	No change	Resection	2 y without Recurrence
5	Wang et al 2007(9)	52	F	Not stated	#11 to #13 area	No symptom/depression of Anterior hard palate	Unilocular Radiolucency	Partial maxillectomy, #16 to #23	No information
6	Afroz et al 2013(10)	20	F	12	Labial gingiva of #12	No symptom /gingival swelling	Non ossifying Soft tissue mass	Total excision	6 mo without Recurrence
7	Chen et al 2014(4)	40	F	48	#12 to #25 area	Pain and loose teeth/Depression of anterior maxilla	Unilocular Radiolucency	Curettage	5 y without Recurrence
8	Chen et al 2014(4)	58	M	3	#16 to #23 area	Loose teeth /swelling	Multilocular Radiolucency	Partial maxillectomy	10 y Without recurrence
9	Tseng et al 2015(11)	24	M	1	#23 to #25 area	Biting pain and loose teeth/no Swelling	Unilocular Radiolucency	Total excision and tooth Extraction	No information
10	Patankar et al 2021(3)	43	M	Not stated	#43 TO #47	Swelling in his lower right back tooth region	Unilocular Radiolucency	Total excision with peripheral ostectomy	6 mo without recurrence
11	Neetha et al 2019(12)	43	F	Not stated	#21 to 25	Asymptomatic	Unilocular Radiolucency	Total excision with intraoral ostectomy	18 mo showed no evidence of recurrence
12	Wonae et al 016(13)	39	F	Incident finding	#12 to 14	Asymptomatic	Unilocular Radiolucency	Total Excision	No recurrence after 1 mo
13	Wonae et al2016(13)	41	F	Incident finding	#11 to 15	Asymptomatic	Radiolucent lesion with cortical thinning and perforation of palate	Total Excision	No recurrence after 29 mo

Table 1: Master Table of all features of reported cases

Features	Classic variant	Non-calcifying Langerhans cell rich variant
Location	Posterior mandible	Anterior-premolar maxilla
Association with impacted teeth	50% of the cases	None of the cases reported
Radiographic features	Radiolucency with radiopaque calcifications	Radiolucency
Odontogenic epithelial cells	Large sheets or islands with pleomorphic features	Small nests or thin strands with no pleomorphism
Calcifications	Present with Leisegang rings	Absent
Langerhans cells	Absent or very small amount	Substantial amount

Table 2: Contrasting features of Classic and Non calcifying Langerhans cell rich variant of CEOT