Case Report

Noncalcifying clear-cell variant of calcifying epithelial odontogenic tumor: A case report and review

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Abstract

Clear-cell tumors of the head and neck are biologically diverse consisting of benign, malignant and metastatic lesions. These tumors pose a diagnostic challenge. In the oral cavity, these may be derived from odontogenic/nonodontogenic epithelium or from mesenchyme or can be metastatic. Odontogenic tumors with clear-cell change are rare. Calcifying epithelial odontogenic tumor (CEOT) is a rare, benign, locally aggressive odontogenic epithelial tumor affecting the jaw. Here, we report a case of clear-cell variant of CEOT with its histopathological differential diagnosis. A 43-year-old male patient with swelling in his lower right back tooth region showed a well-defined radiolucent lesion with smooth corticated periphery on radiograph. On incisional biopsy, tumor showed small sheets, cords and islands of odontogenic epithelium with nests of clear cells with no evidence of calcification. A final diagnosis of CEOT was established by differentiating other odontogenic and nonodontogenic lesions on the basis of clinical, radiographic, histopathologic and special stain features.

Keywords: Calcifying epithelial odontogenic tumor, clear-cell tumor, clear cells, Langerhans cells, noncalcifying clear-cell variant of calcifying epithelial odontogenic tumor, odontogenic tumor

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INTRODUCTION

Clear-cell tumors of the head and neck constitute around 1%–2% of all head-and-neck neoplasms.[1] These tumors are biologically diverse consisting of benign, malignant and metastatic lesions. Cells appear clear in these tumors due to artifactual or degenerative changes, intracellular edema or due to presence of various cytoplasmic contents.[2] Clear-cell tumors pose diagnostic challenge as these tumors can primarily consist of clear cells or clear-cell change may become more significant with progression of the tumor. In the oral cavity, they can be derived from odontogenic or nonodontogenic epithelium or from mesenchyme or can be metastatic. Cysts and tumors of odontogenic origin though have characteristic histopathological features; they may show clear-cell change and can pose a diagnostic challenge. Odontogenic tumors with clear-cell change are rare.[3] Calcifying epithelial odontogenic tumor (CEOT) is a rare, benign, locally aggressive odontogenic epithelial tumor that affects the jaws. 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.[4] However, CEOT can show

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extensive clear-cell change which can make the diagnosis difficult.[5] Here, we report a case of clear-cell variant of CEOT with its histopathological differential diagnosis.

CASE REPORT

A 43-year-old male patient reported to the department of oral pathology and microbiology with chief complaint of swelling in his lower right back tooth region. Clinical examination did not divulge any obvious abnormality as stated by the patient and the medical history was noncontributory. The past dental history suggested that he underwent surgery in the same region 6 months back. Orthopantomogram revealed a well-defined radiolucent lesion with smoothly corticated periphery in the body of the mandible extending from the distal aspect of 43 to the mesial aspect of 47.

Incisional biopsy from the tumor showed bland connective tissue stroma with small sheets, cords and islands of odontogenic epithelium [Figure 1]. Odontogenic epithelial cells were with prominent intercellular bridges and hyperchromatic nuclei. A conspicuous feature of the lesion was the presence of nests of clear cells [Figures 2 and 3]. These cells were large round-to-oval exhibiting foamy cytoplasm with distinct borders. Globular eosinophilic amyloid-like material was admixed with epithelium in some areas. There was no evidence of calcification throughout the lesion.

The following clear-cell tumors were included in the differential diagnosis of this central clear-cell jaw lesion.

Central mucoepidermoid carcinoma

Mucoepidermoid carcinoma is composed predominantly of cystic spaces and an epidermoid component in a fibrous stroma. It also consists of mucous cells and intermediate cells. Cellular pleomorphism and infiltrative growth is usually seen.[6] The clear cells in MEC typically stain positively with PAS. Special staining for mucicarmine or alcian blue can readily identify the mucous cell population, which is considered diagnostic.

Metastatic renal cell carcinoma

Renal cell carcinoma shows solid masses of clear cells with small eccentric nuclei in an organoid or trabecular pattern. Blood vessels are dilated forming large sinusoids. In addition, the identification of a heterogeneous architecture and a rich dilated prominent sinusoidal vascular network favors metastatic renal cell carcinoma diagnosis.[7] Similarly, the identification of hemorrhage and hemosiderin coupled with pronounced pleomorphism and cytological atypia should alert the clinician to the possibility of metastatic disease.

Clear-cell ameloblastoma

Unusual histologic biphasic patterns with areas of acceptable ameloblastoma (follicular, basaloid and acanthomatous) together with the conspicuous clear-cell component in the ameloblastic follicles warrant the diagnosis of clear-cell variant of ameloblstoma.[8,9] Thus, the presence of typical ameloblastomatous areas will help in arriving at the diagnosis.

Clear-cell odontogenic carcinoma

This tumor is poorly circumscribed and consists of sheets of cells of uniform size with abundant clear cytoplasm and well-defined cell membranes. Tumor islands are separated by relatively dense fibrous tissue septa and may show peripheral palisading. Lesser dense areas of small basaloid epithelial cells with scanty cytoplasm or areas of hemorrhage may also be present.[10-13]

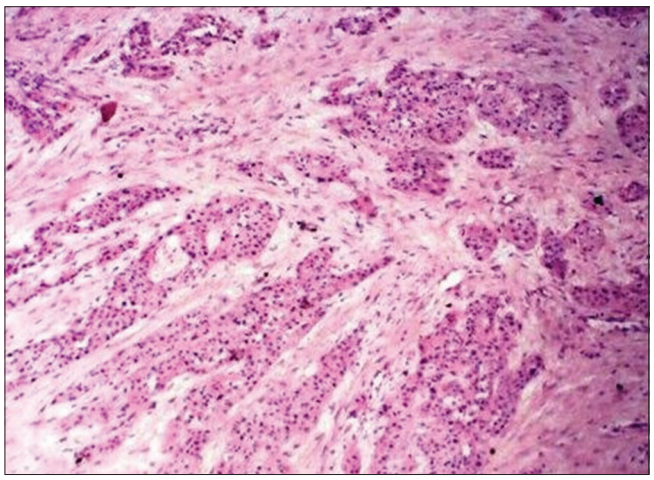

Figure 1: Histopathological image shows sheets of odontogenic epithelium in the stroma arranged in cords and small islands (H&E,×100)

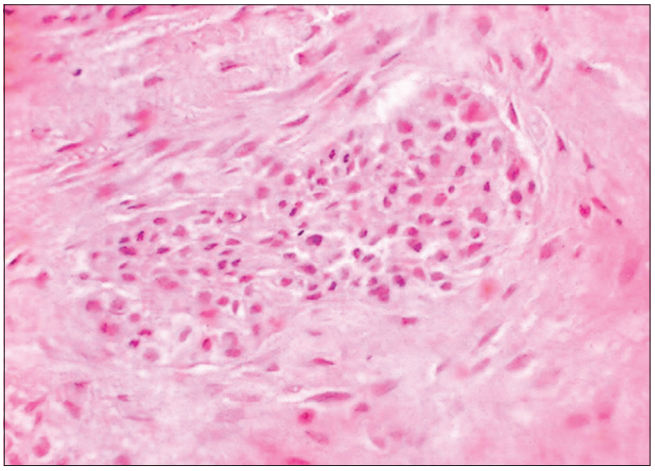

Figure 2: Histopathological image shows sheets of odontogenic cells with hyperchromatic nuclei and prominent intercellular bridges H&E ×400)

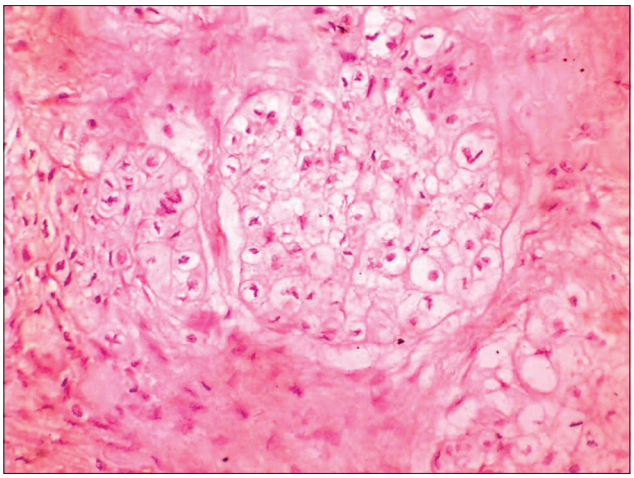

Figure 3: Histopathological image shows nests of clear cells (H&E ×400)

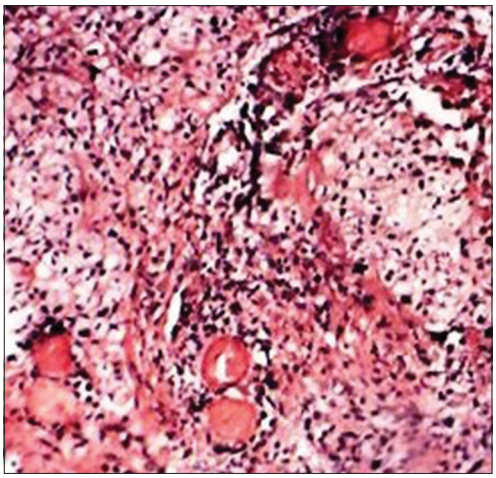

Figure 4: Histopathological image shows amyloid-like material admixed with epithelium (Congo red, ×100)

In our case, lack of clinical and radiographic evidence of malignant disease, absence of microscopic ameloblastomatous differentiation and the unequivocal presence of amyloid material and presence of sheets of odontogenic cells with hyperchromatic nuclei and presence of prominent intercellular bridges helped us to establish the diagnosis of CEOT. Special staining of amyloid-like material with Congo red helped us to confirm the diagnosis of CEOT [Figure 4]. Negative staining with mucicarmine ruled out the salivary gland origin of the tumor. However, the most characteristic feature of CEOT, that is calcifications, was not seen which made the diagnosis more challenging. The absence of calcification and presence of nests of clear cells in the present case were essential features to establish the final diagnosis of noncalcifying clear-cell variant of CEOT. The patient was then referred to the department of the surgery where he underwent excision of the lesion with peripheral ostectomy. The patient was followed-up for 6 months with no evidence of the recurrence.

DISCUSSION

CEOT is a rare, benign, locally aggressive odontogenic epithelial tumor that affects the jaws. First described in 1955 as a separate entity by Pindborg, it usually affects middle-aged individuals, with mandible being the most common site of occurrence.[14] The most distinctive microscopic feature of classical CEOT is the presence of sheets of polyhedral cells, presence of amyloid globules and Liesegang ring calcifications in the tumor tissue. However, the presence of clear cells and absence of calcification in the present case posed a diagnostic challenge. Occurrence of clear cells with a complete absence of calcification has been a rarity being reported in approximately 8% of cases of CEOT.[10,15] Some authors have also described it as a feature of cytodifferentiation.[16,17] Absence of calcification may suggest less differentiation in the tumor. Our case was devoid of calcifications and there were nests of clear cells. Absence of calcification and presence of clear cell could be related here.

The authors have also described noncalcifying clear-cell variant of CEOT as Langerhans cell (LC)-rich variant of it.[18-22] It is suggested that clear cells in noncalcifying CEOT could be LCs. 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.[23] Thus, the presence of clear cells and absence of calcification can also be related to the presence of LCs in odontogenic nests of CEOT.

We reviewed cases of LC-rich variant of CEOT by typing keywords such as LC-rich variant of CEOT; CEOT with LCs; CEOT without calcifications; LC-rich variant of Pindborg tumor; noncalcifying LC-rich variant of CEOT and noncalcifying CEOT with LCs. We found 12 cases of noncalcifying LC-rich variant of CEOT through standard databases. Of these, two cases occurred extraosseously [Table 1]. This variant is commonly seen in the anterior maxilla with unilocular radiolucency without radiopaque foci and root resorption as common radiographic presentation. These cases were not associated with impacted teeth. Based on this finding, Chen *et al*. proposed that LC variant of CEOT may not be derived from reduced enamel epithelium and can have other odontogenic sources for origin such as the rests of Malassez as this

Table 1: Review of cases of noncalcifying Langerhans cell-rich variant of calcifying epithelial odontogenic tumor

Author, years	Age, sex	Clinical features	Radiographic features	Histopath diagnosis	Special stains/IHC findings	Treatment	Follow-up and recurrence
Rangel AL *et al.,* 1990[5]	44, female	Swelling 16-11 area	Unilocular Radiolucency, tooth root Resorption-with 11 to13	Noncalicifying LC rich variant of CEOT	Positive Congo red, crystal violet, methyl violet, thioflavin T, Positive S-100 protein, CD1a, lysozyme, CD43 and HLA-DR	Partial maxillectomy	Not available
Takata *et al*., 1993[24]	58, male	Associated with 23-25 area, Loose teeth	Unilocular Radiolucency with 23 and 25	Noncalicifying LC rich variant of CEOT	Positive S-100 protein, positive Congo red and thioflavin T	Enucleation	10 years without recurrence
Wang *et al*., 2006[25]	38, male	44 to ascending ramus, pain and swelling	Multilocular radiolucency	Calcifying epithelial odontogenic tumor with LCs	Positive CD1a, S-100 protein, HLA-DR and CD68, positive Congo red, positive PAS stain	Partial mandibulectomy	2.5 years without recurrence
Wang *et al*., 2006[25]	39, female	24 months, left upper premolar gingiva, gingival swelling	No change as extraosseous lesion	Extraosseous calcifying epithelial odontogenic tumor with LCs	Positive PAS stain, positive Congo red, positive CD1a, S-100 protein, HLA-DR and CD68	Resection	2 years without recurrence
Tseng CH *et al*., 2007[26]	52, female	11-13 area. No symptoms, depression of anterior hard palate	Unilocular radiolucency, root resorption, with 12 and 13	Noncalcifying LC variant of CEOT	Positive for AE1 and AE3, positive for Congo red, positive for CD1a	Partial maxillectomy	Not available
Kaushal *et al*., 2012[27]	57, male	Difficulty in speaking for 11/2 months	Unilocular lesion measuring 8×4 cm over the right lower jaw, involving the angle of mandible MRI revealed a lesion in the right mandible involving the body and ramus	Noncalcifying epithelial odontogenic tumor	Positivity for cytokeratin	En bloc resection	No recurrence for 1 year
Afroz *et al*., 2013[28]	20-year-old woman	Slowgrowing hard mass in the right upper region since 1 year, a hard nodule measuring 1 cm in diameter, located just above the right lateral incisors	Extraosseous lesion	Extraosseous, noncalcifying variant of CEOT harboring LCs	Positivity for cytokeratins AE1 and AE3, and the clear cells showed S-100 positivity suggesting them to be LCs	Excised	The tumor has not recurred 6 months after excision
Chen *et al*., 2014[29]	40, female	Pain and loose teeth with 12-25 area, depression of anterior maxilla	Unilocular Radiolucency with resorportion of 21 and 22	LC variant of CEOT	Positive for Congo red, LCs positive for langerin, S-100 and CD1a were seen in the epithelial islands of the tumor, The ratio of LCs to epithelial tumor cells was 82.7:100	Curettage	5 years without recurrence
Chen *et al*., 2014[29]	58, male	Swelling in the right maxilla 3 months ago, loose teeth with swelling with 16-23 area	Multilocular Radiolucency with resorption of 13-16	LC variant of CEOT	LCs positive for langerin, S-100 and CD1a were seen in the epithelial islands of the tumor, The ratio of LCs to epithelial tumor cells was 42.1:100	Partial maxillectomy	10 years without recurrence

Contd.....

Table 1: Contd....

Author, years	Age, sex	Clinical features	Radiographic features	Histopath diagnosis	Special stains/IHC findings	Treatment	Follow-up and recurrence
Tseng *et al*., 2015[30]	24, male	1 month, 23-25 area. Biting pain and loose teeth/no Swelling	Unilocular Radiolucency, resorption of roots of 23-25	Noncalcifying LC rich variant of CEOT	Positive for Congo red, positive for CD1a and S-100 protein	Total excision and tooth Extraction	Not available
Taneeru *et al*., 2017[31]	27, female	Painless swelling in the lower left back tooth region. Single, left submandibular lymph node was palpable	Multilocular radiolucency extending from 36 to 38 region posteriorly with irregular borders was seen. Unerupted 37 and mesial migration of 38 have been noticed-final diagnosis of noncalcifying type of CEOT was confirmed	Noncalcifying type of CEOT	Not done	Wide surgical excision of tumor, reconstruction with iliac crest graft	No evidence of recurrence for 2 years
Santosh *et al*., 2018[32]	43, female	Asymptomatic with no bony expansion or paresthesia	Large radiolucent lesion involving the left anterior maxilla	Noncalcifying LC rich variant of CEOT	Positive for Congo red, the epithelial cells were strongly and diffusely positive for Pancytokeratin-MNF-116, Scattered CD1a- and Langerin-positive LCs were present	Surgical excision of the tumor with intraoral osteotomy	No evidence of recurrence for 18 months

CEOT: Calcifying epithelial odontogenic tumor, LC: Langerhans cell, IHC: Immunohistochemistry

variant was found to cause root resorption of the apical part of the involved tooth. Histopathologically, this variant shows smaller islands and cords of odontogenic cells with the presence of abundant amyloid substance. These cases show no evidence of calcifications and presence of clear cells, unlike conventional CEOT. Odontogenic origin of epithelial cells can be confirmed by positive cytokeratin staining. Further, the presence of LC can be confirmed with positive expression of S-100, langerin and CD1a.[18,29] In our case, after through sectioning of the entire specimen, we found no evidence of calcification and there were nests of clear cells. However, we could not immunohistochemically confirm the presence of LCs.

The authors suggest that noncalcifying LC-rich variant of CEOT can behave differently. According to some authors, this variant of CEOT can have an aggressive behavior as the absence of calcifications suggests less tumor differentiation.[32] In our case also, the present lesion was a recurrent lesion though details regarding earlier treatment modality are lacking. However, none of the cases reported in literature have shown recurrence. According to Asano *et al*., LCs may play a role in the regression of CEOT as it is found in halo nevi, keratoacanthomas and benign lichenoid keratosis.[33] However, more cases are required to be studied to determine the relation between the absence of calcification and presence of LC in CEOT and its biologic behavior with longer follow-ups.

CONCLUSION

Noncalcifying clear-cell variant of CEOT represents a rare subset of neoplasms. The occurrence of clear cells in a field devoid of calcification and minimal features of the conventional CEOT can lead to a diagnostic dilemma which needs careful histopathological evaluation. The need to identify these lesions is attributed to its biologic behavior and implementation of appropriate therapy.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initial s will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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