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CASE REPORT

Signet ring clear cell variant of Calcifying Epithelial Odontogenic Tumour: A Rare histopathological Presentation

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Abstract
Calcifying epithelial odontogenic tumour (CEOT) is an uncommon, benign, odontogenic neoplasm that is epithelial in origin. It accounts for 1% of all the odontogenic tumors of the jaws. Conventionally, CEOT on histological examination exhibits sheets and islands of polyhedral cells with abundant finely granular eosinophilic cytoplasm with well-defined cytoplasmic borders and prominent intercellular bridges. Characteristic homogenous eosinophilic amyloid and calcifications either focally or in the form of liesegang rings are noted frequently. Various histologic variants have been described; among which clear cell variant is a rare one. Here we present an unusual case of intraosseous large CEOT with signet ring clear cells.
Keywords: Calcifying epithelial odontogenic tumour, Odontogenic Epithelial tumour, Clear cell, Signet ring cell, induction, amyloid, Leisegang rings

1 | INTRODUCTION

Calcifying epithelial odontogenic tumour (CEOT) was first described by Late Dr Jens J Pindborg in 1956 [1]. It was identified under different terminologies like ameloblastoma of unusual type with calcification, calcifying ameloblastoma, malignant odontoma, cystic complex odontoma and was also considered as a variant of simple ameloblastoma [2]. CEOTs account for about 1% of all odontogenic tumors. It is a typically benign and slow growing, but invasive neoplasm [3]. It has been defined by the World Health Organization, as "a locally invasive epithelial odontogenic neoplasm, characterized by the presence of amyloid material that may become calcified" [4]. The origin of this neoplasm is controversial, though it is generally accepted to be derived from the oral epithelium, reduced enamel epithelium, stratum intermedium or dental lamina remnants. Clinically, to the intraosseous variant (94%) is more common than the extraosseous type (6%) [2]. The age of occurrence of CEOT is 40-50 years with equal sex predilection. It usually occurs in the posterior mandible as a painless swelling frequently associated with impacted tooth. Radiographically, it is seen

as a unilocular or multilocular radiolucency with flecks of radioopacity giving a "driven snow' appearance [1].

The classical histolopathological findings include sheets and islands of polyhedral odontogenic epithelial cells with well-defined cytoplasmic borders, prominent intercellular bridges and frequent nuclear pleomorphism. Amorphous eosinophilic homogeneous amyloid – like material and either focal or large amounts of calcification in the form of Liesegang rings are frequently seen [5]. Sometimes, focal areas of clear cells can be seen in clear-cell variant of CEOT (CCCEOT) [2]. It is a rare variant and reported in 8% of all CEOTs [6].

Here we describe a unique case of CEOT in a 60 year old female Indian patient involving the posterior mandibular segment with clear cell change exhibiting signet ring appearance histologically.

2 | CASE REPORT

A 60-year-old female patient presented to the outpatient department with a chief complaint of painless swelling in the lower right posterior teeth region which became noticeable since a year. The swelling was small in size and gradually increased to the present size over a span of few years (3-4 years). The patient had a habit of eating areca nut and betel leaf since 20 years with a frequency of 10-12 times/ day. The patient also had a medical history of diabetes since 8 years and was on medication and responding well.

On extra-oral examination, there was a facial asymmetry due to solitary, diffuse, oval shaped bony hard swelling of the mandible on the right side measuring about 4.0x3.0 cms. The lesion extended superoinferiorly 1.0 cm below the line joining the corner of the mouth and tragus till 2.0 cms beyond the lower border of the mandible. Antero-posteriorly the lesion extended from commissural area to the angle of the mandible. The colour of the overlying skin was normal. On palpation the lesion was firm, non-tender, non- compressible, non-pulsatile and fixed to the underlying tissues. There was no raise in the surface temperature or any surface changes except the skin changes that appeared stretched and smooth (Figure 1 a).

On Intra-oral examination, there was an intra-osseous swelling extending from mesial aspect of 42 to 48 teeth and ramus region. The swelling had a smooth surface with both buccal and lingual cortical expansion and obliterating the buccal and lingual sulci. The swelling was smooth surfaced, hard, non-tender and approximately measuring 6.0x 4.0 cms. (Figure 1 b) There were no surface mucosal changes except being stretched and blanched at areas. All the teeth showed extensive occlusal attrition and stains. There was no mobility of the involved teeth but the involved teeth 48, 47,46 and 45 were non-vital. There was also slight mesial drift of 44 and 43 teeth. The right and left submandibular lymph nodes were firm, mobile and palpable.

Based on the above clinical findings a range of benign tumours like ameloblastoma, odontogenic myxoma, and CEOT were considered for diagnosis. The malignant tumours like primary intraosseous carcinoma, central ossifying fibroma and central mucoepidermoid carcinoma were also considered as differential diagnosis.

A panoramic radiograph (OPG) revealed a large, ill-defined, mixed radiopaque-radiolucent lesion exhibiting ground glass appearance. The lesion extended from distal aspect of 41 to ramus of the mandible till 1.0 cm below the sigmoid notch. There was slight displacement of teeth 44 and 45 and the lower border of the mandible was blown off with inferior displacement of mandibular canal (Figure 2 a). The occlusal radiograph confirmed both the buccal and lingual cortical expansion exhibiting ground glass appearance with small honeycomb like loculi.

Supplementary information The online version of this article (https://doi.org/10.15520/ijmhs.v10i03.286) contains supplementary material, which is available to authorized users.

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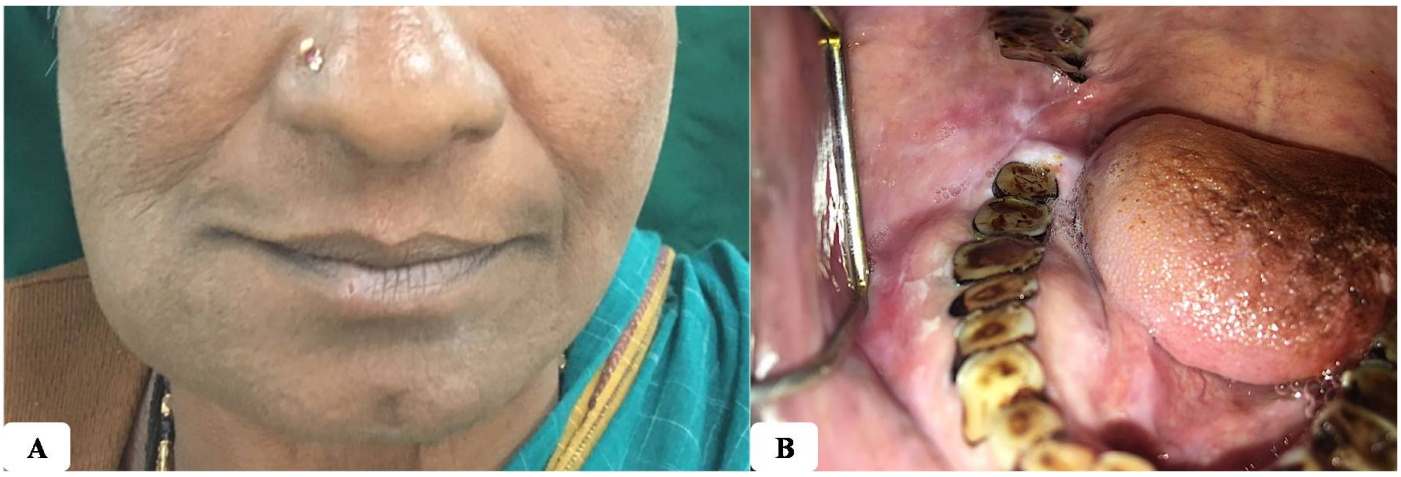

FIGURE 1: A. Extra-oral photograph showing facial asymmetry with a swelling on the right side of the face. B. Intraoral swelling involving the teeth 41 to retromolar area and obliterating the buccal and lingual sulcus. Tobacco stains on tongue and hyperkeratotic areas seen in retromolar region.

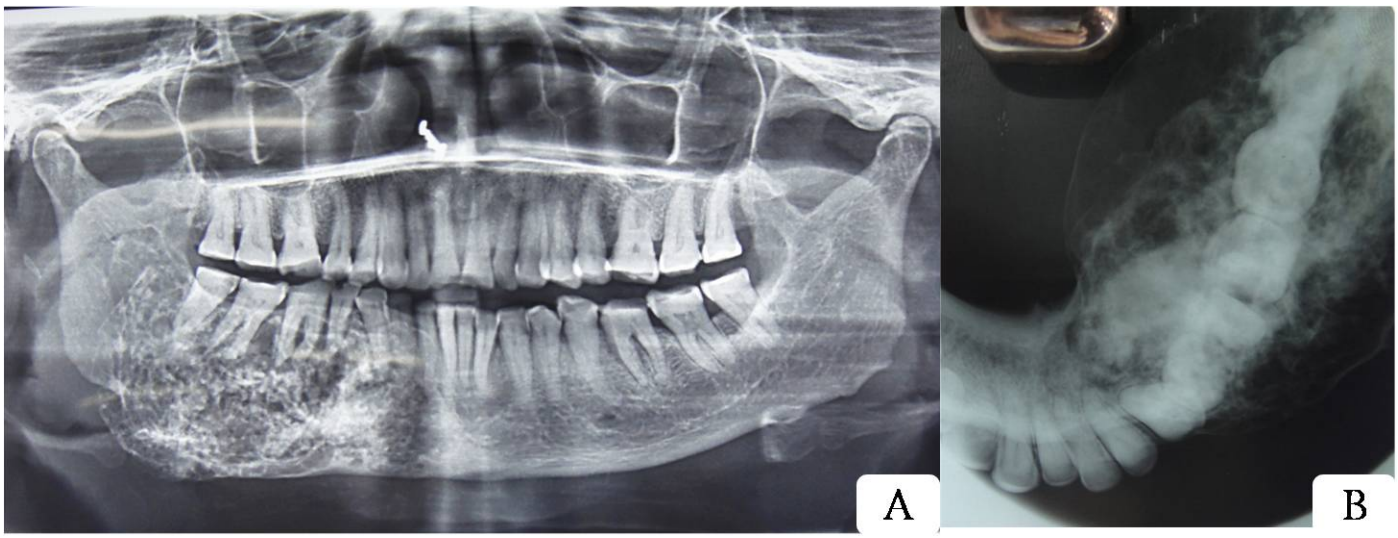

FIGURE 2: A. Orthopantomograph showing large, ill-defined lesion with ground glass appearance involving the right ramus of mandible, extending anteriorly to the right central incisor (41), involving the lower border of the mandible and ramus. B: The occlusal radiograph showing both the buccal and lingual cortical expansion exhibiting ground glass appearance.

(Figure 2 b)

Advanced imaging computed tomography (CT) showed a destructive lesion with cortical expansion on both buccal and lingual aspect of the mandible. The lesion showed multiple opacities within them. The lingual cortex was thinner than the buccal cortex (Figure 3). There was a slight distobuccal drift of 48.

Incisional trephination biopsy was done under local anesthesia wherein hard and soft tissue bits were received. The soft tissue bits were creamish brown in color, irregular in shape and firm in consistency measuring approximately 0.7x0.7 cms in size. (Figure 4 a & b)

The histopathological examination of H & E stained tissues showed unencapsulated lesional tissue made of sheets, island and nests of odontogenic epithelial cells with extracellular scattered amyloid like material and dystrophic calcifications. The epithelial cells were round to polygonal in shape with prominent cellular outlines, intercellular bridges, ample

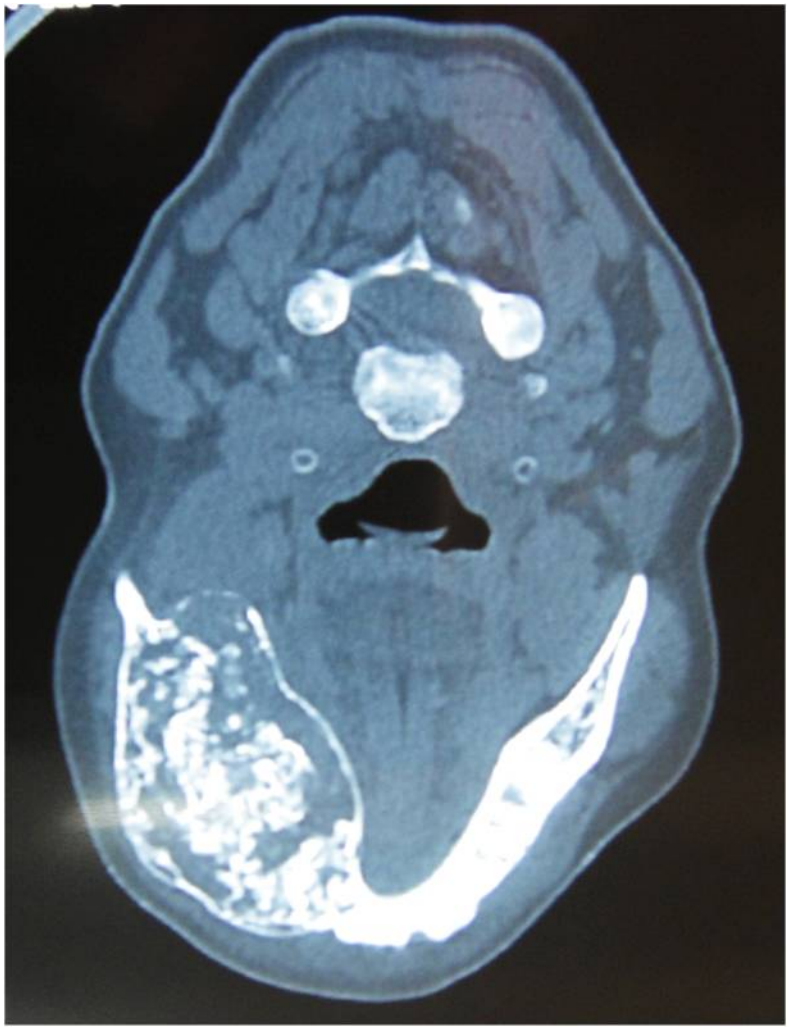

FIGURE 3: Computed tomography image of the lesion showing a destructive lesion with cortical expansion on both buccal and lingual aspect and radio-opacities within the lesion. The lingual cortical plate shows fenestrations.

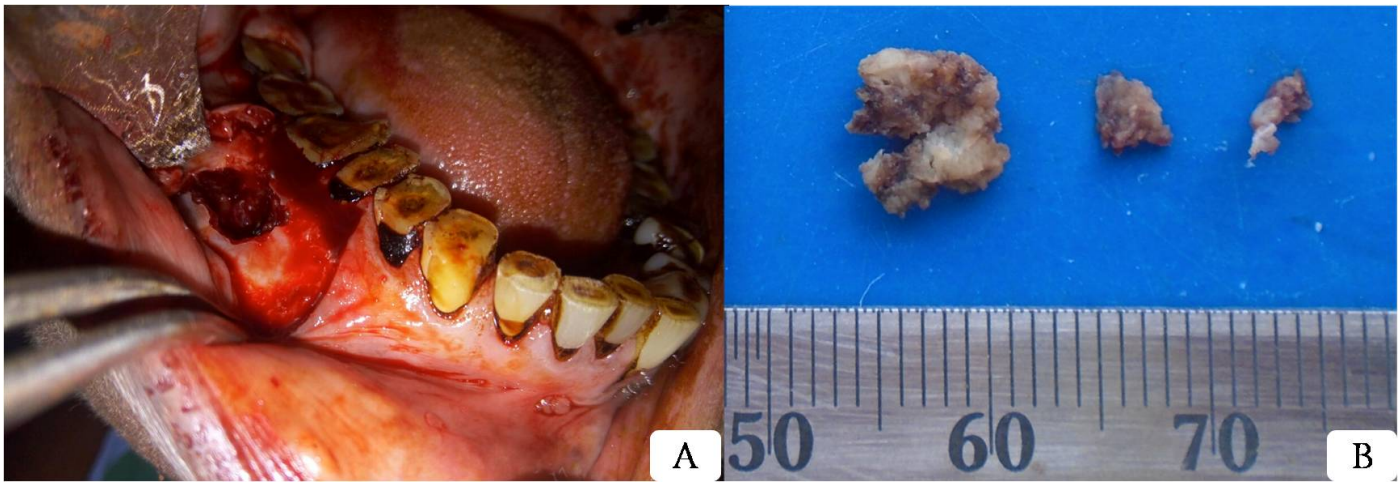

FIGURE 4: A. Intra-operative photograph demonstrating the site of incisional trephination biopsy. B. Grossing image of incisional biopsy soft tissue specimen which are creamish brown in colour, irregular in shape and firm in consistency.

eosinophilic cytoplasm exhibiting nuclear and cellular pleomorphism. Interestingly, there was no evidence of any mitosis. Another exciting feature found was presence of epithelial cells exhibiting vacuolisation with few of them showing peripherally pushed nuclei resembling "signet ring" cells (Figure 5 a, b &c).

Extracellular amyloid-like material and multiple cystic spaces of varying sizes filled with homogenous eosinophilic amyloid like material seen throughout the lesion was positive for congo red stain (Figure 6 a) which showed apple–green birefringence under polarized light. The special stain PAS did not stain the extracellular eosinophilic amyloid like substance and signet ring like cells. Few calcifications showed positivity (Figure 6 b). Ki-67 immunostaining showed nuclear positivity in the odontogenic epithelial cells and the Ki index was 20-30% (Figure 6 c).

Thus a diagnosis of Calcifying epithelial odontogenic tumour was made. Right hemimandibulectomy was done as a treatment procedure under general anaesthesia and the mandible on the right side extending from distal aspect of lateral incisor mesially to retromolar area distally, about 1 cm away from mandibular notch was removed (Figure 7 a). The histological findings were similar to the histopathological features seen on incisional biopsy. The bone adjacent to the lesional tissue showed a rim of plump osteoblastic lining confirming the benign nature of the lesion. The decalcified sections showed presence of calcifications in the form of Leisegang rings associated with amyloid like material and odontogenic epithelial cells displaying nuclear pleomorphism (Figure 7 b)

3 | DISCUSSION

CEOT is a benign, slowly growing, locally invasive epithelial odontogenic tumour that was first described by Pindborg in 1955. It is predominantly an intraosseous tumour but it can also occur as a rare peripheral/ extraosseous tumour which less aggressive than the intraosseous [2] . The histogenesis of this tumor is still obscure. It is suggested that it can arise from the stratum intermedium layer of the enamel organ or remnants of dental lamina [7, 8].

The age of occurrence for CEOT ranges between 8 and 92 years and the average being 38.9 years [2]. Whereas the age range for clear cell variant of CEOT (CCCEOT) is between 14 and 68 years with a mean age of 41.5 years. The mean age of intraosseous variant is higher (46.3 years) than the extraosseous variant (34.3 years) [9]. Females are more affected than males in the intraosseous variant of CCCEOT with a ratio of 2:1. In our case, the patient's age is 60 years and is a female which is in accordance to the Thomas J et al [9].

According to Philipsen and Reichert, the intraosseous CEOTs are frequently seen in the mandible, with 82% being located in the premolar and the molar region [2]. Our current case also was seen in posterior region of the right mandible involving the molars.

It usually presents as a painless swelling and in about 52% of the patients they are associated with impacted/ unerupted tooth [1]. In our case the patient also had a painless swelling, but it is not associated with any impacted tooth.

Radiographically, the lesion can be unilocular or multilocular with numerous scattered radioopaque foci of varying sizes and densities giving a "driven snow appearance" [9].CEOT can displace or prevent the eruption of tooth, and associated expansion of the jaw with intact cortical boundary can be seen [10].

In contrast, the radiographic findings of our case exhibited ill-defined borders with a ground glass appearance where the cortical borders were not intact and the lower border of the mandible was blown off. This is in accordance to analysis done by Yakir Anavi et al who found that cortical perforation is more common in clear cell variant than the conventional CEOT [11].We also found a mild mesial drift of 43 and 44, but there was no resorption of any of the involved teeth.

The characteristic histologic findings of CEOT shows sheets, islands or strands of odontogenic epithelial cells that are polyhedral and pleomorphous with abundant eosinophilic cytoplasm and prominent intercellular junctions. Nuclei exhibit Pleomorphism and hyperchromasia. Amorphous eosinophilic amy-

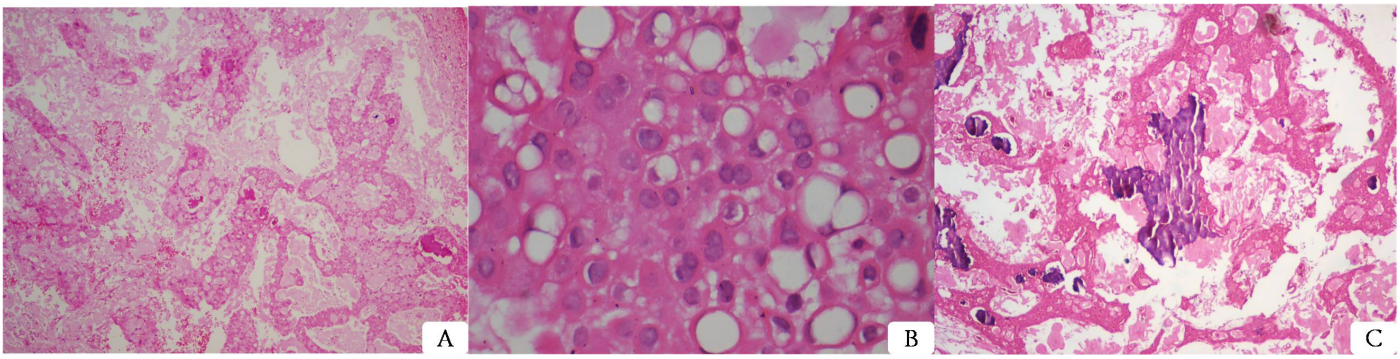

FIGURE 5: A: Photomicrograph showing sheets and islands of odontogenic epithelial cells, scattered amyloid like material and leisegang calcifications (H&E stain x40). B: Photomicrograph showing round to polygonal epithelial cells with prominent cellular outlines, intercellular bridges, exhibiting nuclear and cellular pleomorphism with few nuclei showing vacuolated cytoplasm with peripherally placed nuclei- ``Signet-ring'' change. (H&E stain x200). C. Photomicrograph showing numerous dystrophic calciifcations scattered throughout the sheets of epithelial cells. H&E stain, x40

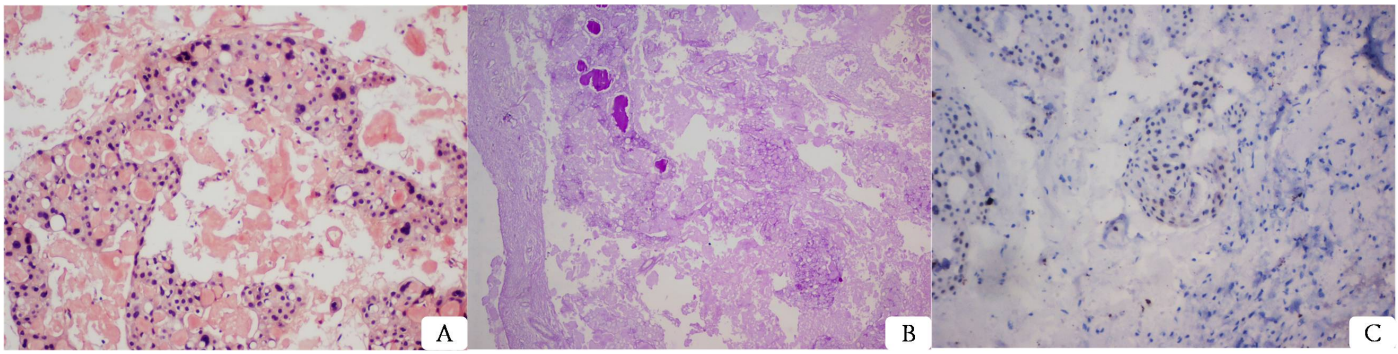

FIGURE 6: A. Photomicrograph showing extracellular homogenous eosinophilic amyloid- like material positive for congo red stain (Congo red stain, x100). Congo red stainx100. B. Photomicrograph showing PAS negativity for amyloid like substance and signet ring like cells. Calcifications were positive (PAS stain x40). C. Ki-67 showing mild nuclear positivity with the index being 20-30% (IHC stain, x40)

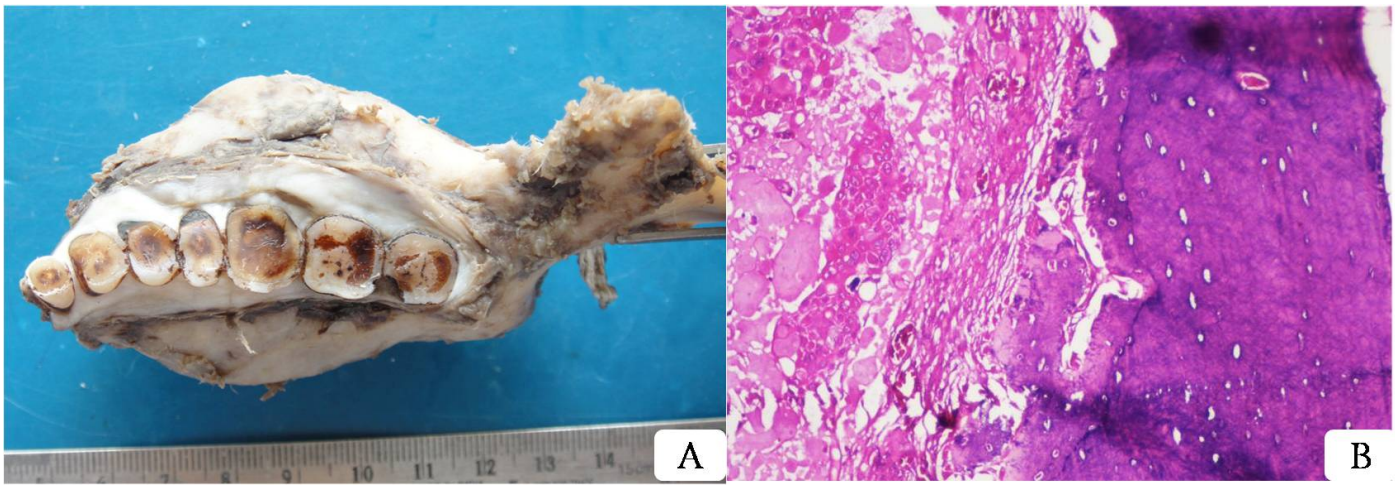

FIGURE 7: A.Gross hemi-mandibulectomy specimen. B.Photomicrograph showing mature bone with prominent osteoblastic rimming adjacent to the lesional tissue (H&E stain x40).

loid like material and concentric liesegang ring calcifications within the amyloid material is seen as a characteristic feature. In addition, presence of clear cells, langerhans cells, myoepithelial cells associated with CEOT have been reported in the literature [8, 12].

In our current case, classical histological findings with the epithelial component predominating compared to amyloid like material and dystrophic calcifications was seen. Apart from these findings, there was also presence of epithelial cells exhibiting clear to vacuolated cytoplasm with a peripherally pushed nucleus giving it a signet ring appearance. Based on these findings a diagnosis of "Signet Ring" clear cell variant of CEOT was made.

A clear cell variant of CEOT is well recognised and was first reported by Abrams and Howell in 1967 [13]. Clear cell variant of CEOT is a rare subset, which has been reported in approximately 8% of CEOTs [6]. In odontogenic lesions we can find clear cells which were thought to be originating from dental lamina remnants [14]. The exact nature of these clear cells in CEOT is not yet established. Generally, clear cells are seen in various tumours and could be a result of artefacts due to fixation, accumulation of glycogen, mucin, lipid in intracytoplasmic location and can also can result due to scarcity of organelles. According to some authors, the intracytoplasmic glycogen accumulation causes the clear nature of cells observed in CCCEOT and predominantly the clear cells of CCCEOT were PAS positive, had centrally located round hyperchromatic nucleus and immunoreactive for EMA and cytokeratins [15, 16].

In contrast to the above findings, the clear cells of the current case were PAS negative and mildly positive for Ki-67 pointing towards the benign nature of the lesion. We are in accordance to Yamaguchi et al. who hypothesised that clear cells represent a feature of cytodifferentiation associated with a simple degenerative phenomenon [17].

The histological differential diagnosis for clear cell variant of CEOT includes the lesions that are odontogenic, salivary gland and metastatic tumours with a prominent clear cell component. They include central mucoepidermoid carcinoma (clear cell variant), acinic cell carcinoma, metastatic tumours from kidneys and other odontogenic tumours such as ameloblastoma with clear cell changes and clear cell odontogenic carcinoma (CCOC). This variant of CEOT poses a diagnostic challenge especially in incisional biopsies and it is of utmost importance to diagnose this lesion as it has a different biologic behavior compared to the malignant tumours.

MEC at focal areas exhibits solid nests of tumour cells consisting of a mixture of epidermoid, intermediate and mucous cells which would be PAS positive. Our case was negative for PAS. Acinic cell carcinoma shows microcystic or follicular pattern and it has the characteristic cytoplasmic diastase-resistant PAS-positive secretory zymogen granules which is not seen in CCCEOT.

The metastatic renal cell carcinoma unlike CCCEOT microscopically shows small islands of clear cells with distinct capillary septa and is a richly vascular tumour.

Ameloblastoma with clear cell changes atleast focally shows peripheral tall columnar ameloblast-like cells exhibiting reversal of polarity of nuclei and central stellate-reticulum like cells which is not seen in CCCEOT.

Presence of congo red positive amyloid and variable amounts of calcifications (Leisegang rings) helped us to differentiate CCCEOT from CCOC. According to Bilodeau et al, a significant proportion of CCOCs had EWSR1 translocations [18]. Overall, lack of cellular atypia, mitotic figures, presence of amyloid-like material and calcified Leisegang rings were the vital features to establish a final diagnosis of clear cell (signet ring) variant of CEOT.

Treatment for this lesion ranges from simple enucleation/ curettage to extensive radical resections [11].

According to Hicks et al. CEOT with clear cell change can have a more aggressive behavior than the conventional counterpart and thus should be dealt with caution and treated with more radical approach.Large CEOTs should be treated either by segmental resection or hemimandibulectomy with reconstruction procedures [19].

Few cases of CCEOT with clear cell change had recurrences which could be due to inadequate surgical

removal either by curettage or partial resection [15] . In our case, right hemimandibulectomy was performed. The patient was kept under regular follow-up and showed no recurrence on 10 month follow-up.

In summary, we report a rare case of "Signet ring" clear cell variant of CEOT. Our reported case responded well to surgical treatment i.e., hemimandibulectomy with no sign of recurrence. For better understanding regarding the biologic behavior of this clear cell variant of CEOT, many more cases need to be reported.

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