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CALCIFYING EPITHELIAL ODONTOGENIC TUMOUR - CASE SERIES FROM FIVE NIGERIAN TEACHING HOSPITALS
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ABSTRACT

***Background*: Calcifying epithelial odontogenic tumour (CEOT) also known as Pindborg's tumour is a relatively rare odontogenic neoplasm of epithelial derivation that constitutes about 0.4-3% of all intraosseous odontogenic tumours.**
***Objectives*: To document all cases of CEOT encountered in five tertiary centres in Nigeria and their clinical, radiologic and histologic characteristics.**
***Design*: A retrospective study.**
***Setting*: Tertiary Dental Facilities in Lagos, Ibadan, Ife, Port Harcourt and Zaria (all in Nigeria) were involved in the study.**
***Subjects*: All odontogenic tumours (OTs) in the period from 1970 -2014. Case file records and biopsy reports were retrieved from the records of the five Teaching Hospitals, to obtain age, gender, location, size, clinical symptoms, pathological reports and radiographic description.**
***Results*: Out of a total of 1369 OTs, 20 (1.5%) cases of CEOT were reported. CEOT had a male to female ratio of 1.9:1, with mandible: maxilla ratio of 1.5:1 and the most common location being the premolar /molar region in the mandible. Nine (45%) cases appeared radiolucent while 11(55%) cases had mixed radio density. The mean diameter for mixed radio-dense lesions (4.83±2.99) was higher than that for radiolucent lesions (2.75±1.17) and the difference was statistically significant (p=0.049).**
***Conclusion*: CEOT is a rare tumour representing 1.5% of OTs. CEOT presents with some subtle geographic differences in its demography, however, further studies are required to investigate if these differences are coincidental or genetically determined.**

INTRODUCTION

Calcifying epithelial odontogenictumour (CEOT), also known as Pindborg's tumour is a relatively rare odontogenic tumours (OT) of epithelialderivatives, which constitutes about 0.4-3% of all intraosseous odontogenic tumours (1). Pindborg initially identified CEOTin 1958 (2), although,the term 'unusualameloblastoma' was previously used by Ivy to designate CEOT(3). Up until the year 2000, 181 cases of CEOT were reported in the scientific English literature (4). Although benign, it may present a locally aggressive nature and cause destruction of bone (4). CEOT may present with extreme morphologic variations and severe cellular abnormalities thereby mimicking a malignant lesion that requires a more radical treatment (5). On the other hand, the clinical and radiological presentations of CEOT may mimic those of other odontogenic tumours like ameloblastoma or even dentigerous cyst that are not as aggressive as CEOT and therefore requiresless aggressive treatment (6). Misdiagnosis of CEOT invariably results in in-appropriate surgical management that could lead to devastating consequences.

The information on the clinicopathological

and radiological features of CEOT in Nigerians is insufficient but its' prevalence in Nigeria in relation to odontogenic tumours has been documented in various studies (7-11). CEOT is a relatively rare odontogenic tumour and many reports on the tumour are from small case series (12-16). Multi centre studies are therefore desirable to obtain and study a larger population and thus add to the knowledge of its clinical and histologic characteristics. The present study therefore aims to examine clinical, radiologic and histologic characteristics of all cases of CEOT encountered in five tertiary centers in Nigeria.

MATERIALS AND METHODS

All odontogenic tumours reported during the period from 1970 -2014 were retrieved from the records of the University Teaching Hospitals of Lagos, Ile-Ife, Ibadan, Port Harcourt, and Zaria. Hematoxylin and eosin stained histological slides of all cases that had a diagnosis of CEOT were reviewed for confirmation and included. The cases that could not be reviewed by histology confirmation and those with inadequate clinical details were excluded. Researchers in each center retrieved case files and biopsy records to obtain age, gender, location, size, clinical symptoms and radiographic description (which comprised of the lesion definition, locality, radiographic density and presence/absence of impacted teeth within the lesion). These parameters were documented as guided by a proforma designed by the researchers. The estimated tumour volume (obtained by standardised clinical estimated tumour sizes from the patients records) was computed using the equation 4/3 x 22/7 x radius3. Tumour radius was computed as half the length of the largest diameter recorded for a tumour, based on the assumption that the tumour is spherical.

Data from all the centres was collated at the University College Hospital, Ibadan by two researchers. The data were entered into and analysed with the SPSS software version 12. Simple descriptive and comparative analyses were done, students t-test was used compare means between two groups, with the statistical significance set at $p \leq 0.05$.

RESULT

A total number of 663 (Lagos), 127 (Ife), 68 (Port-Harcourt), 332 (Ibadan), 179 (Zaria) odontogenic tumours were documented during the period under study. Out of these, 20 cases of CEOT representing 1.5% of total OTs were seen. The clinical and radiological data obtained are summarised in Table 1. CEOT was more common in males with a male to female ratio of 1.9:1. The tumour had a slight mandibular predilection (mandible / maxilla = 1.5:1) and was more commonly located in the premolar / molar region in the mandible but frequently extended from incisor to the molar region in the maxilla. Ameloblastoma, dentigerous cyst, odontogenic myxoma, and ossifying fibroma were the variously reported clinical diagnosis prior to histological diagnosis.

With conventional radiography, nine (45%) cases appeared radiolucent while 11(55%) cases had mixed radio-density (radio-opacity and radiolucency). All tumours that presented with mixed radio-density were multilocular while only 22.2 % of radiolucent lesions were multilocular. The mean diameter for mixed radio-dense lesions (4.83±2.99) was higher than that for radiolucent lesions (2.75±1.17) and this difference was statistically significant (p=0.049). Five (25%) cases were associated with impacted teeth consisting of two third molars, one first molar and a case in a 55 year old man that had a canine and a premolar tooth impacted.

There were two notable histological patterns of presentation. The solid pattern consisted of sheets and islands of eosinophilic polyhedral neoplastic epithelial cells within a fibrous stroma. The neoplastic epithelial cells presented with well-defined cell borders and distinct intercellular bridges (Figure 1), with mild nuclear pleomorphism. Some epithelial cells presented with huge hyperchromatic nuclei or multiple nuclei. In addition, some areas within the neoplastic epithelial cells contained amorphous and homogenous eosinophilic material.

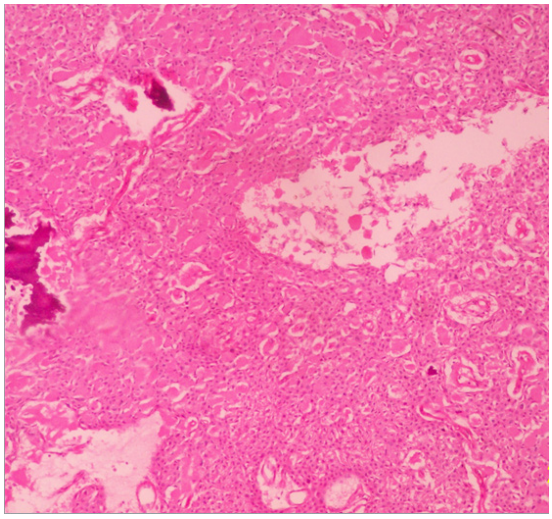
The cribriform pattern consisted of polyhedral neoplastic epithelial cells that had very prominent intercellular bridges and cellular outlines. These were arranged in sheets with numerous spaces present within them. Occasionally some of the homogenous material scattered among the epithelial cells appeared to undergo some degree of calcification and presented as irregular calcified masses similar to osteo-dentin. Congo red special staining technique demonstrated positive reaction to presence of amyloid –like material in all the cases (Figure 2).

Table 1
Overview of CEOT cases seen in all centers

S/N	Gender	Site	Locularity	Radio-density	WdC	Impacted Teeth	Symptoms	Duration (months)	Volume (4/3 x 22/7 x r3) cm^3
1	Male	Mand	Multilocular	Radiolucent	WdC	3rd molar	Painless	12.0	179.2
2	Male	Mand	Unilocular	Radiolucent	WdNotC	Nil	Painless	24 .0	54.2
3	Male	Mand	Multilocular	Radiolucent	WdNotC	Nil	Painless	24.0	522.5
4	Male	Max	Unilocular	Radiolucent	WdNotC	Nil	Painless	12.0	33.4
5	Male	Max	Unilocular	Radiolucent		Nil	Painless	24.0	112.9
6	Female	Mand	Multilocular	Mixed	WdNotC	Nil	Painless	60.0	522.5
7	Male	Max	Unilocular	Radiolucent	WdNotC	1st molar	Painless	12.0	33.4
8	Male	Mand	Unilocular	Radiolucent	WdC	Nil	Painless	12.0	86.9
9	Female	Mand	Unilocular	Radiolucent	WdC	Nil	Painless	12.0	267.5
10	Male	Mand	Multilocular	Mixed	WdNotC	Nil	Painless	48.0	522.5
11	Male	Max	Multilocular	Mixed	WdC	Canine/premolars	Painless/proptosis	408.0	1763.4
12	Female	Max	mulilcular	mixed	WdC	Nil	painless	N/A	
13	Male	Max	multilocular	mixed		Nil	painless	N/A	
14	Female	Mand	multilocular	mixed	WdC	Nil	painless	N/A	65.3
15	Male	Max	multilocular	mixed	WdNotC	Nil	painless	N/A	65.3
16	Female	Mand	multilocular	mixed	WdNotC	3rd molar	Moderate pain	24.0	17.1
17	Male	Mand	multilocular	mixed	WdC	Nil	Moderate pain	9.0	76.5
18	Female	Mand	multilocular	mixed	WdNotC	Nil	Painless/	24.0	
19	Male	Mand	multilocular	mixed	WdC	Nil	Painless	60.0	4180
20	Female	Max	unilocular	Radiolucent	WdC	canine	painless	6.0	33.4

Max=Maxilla, Mand=mandible, WdC= Well defined /Corticated ,WdNotC = Well defined /Not corticated, N/A=Not available.

Figure 1
shows islands and sheet of polyhedral epithelial cells with eosinophilic cytoplasm with large nuclei. The cells have well defined margins with prominent intercellular bridges. There are isolated areas of calcific materials. (H&E x40 and x100)



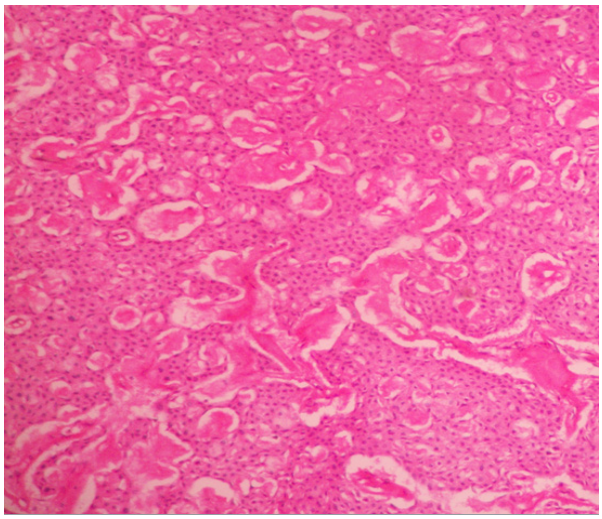
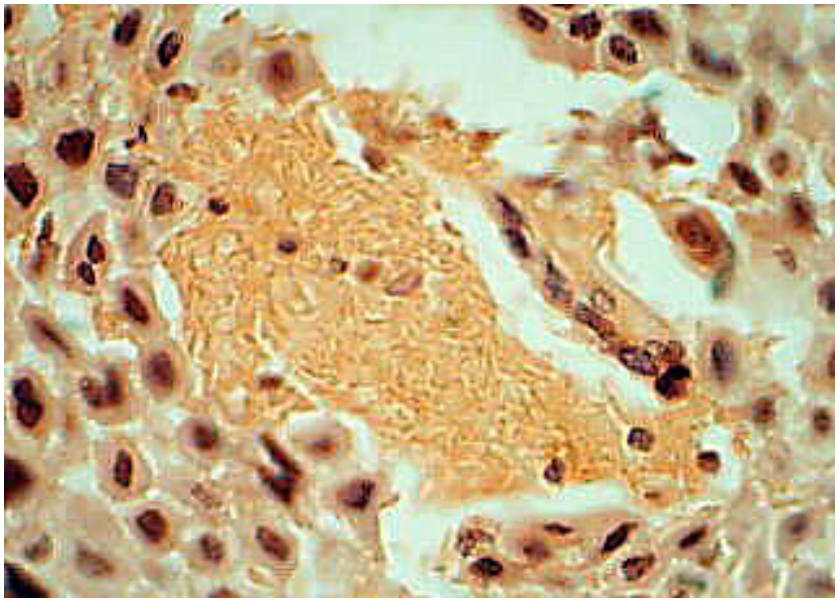


Figure 2

Congo red positive reaction showing reddish homogenous material (arrow) enclosed by polyhedral epithelial cells . The cells have abundant eosinophilic cytoplasm and showed variation in nuclear size and shape. Congo Red stain X1000



DISCUSSION

Pindborg's tumour (CEOT) was first categorised as a distinct histopathologic entity in 1958 (2). The low frequency of occurrence of CEOT (1.5% of total OTs) that was observed in our present study, agrees with previous studies, which reported CEOT to be a rare OT (1-4). According to Franklin and Pindborg (12), from a total of 2412 odontogenic tumours in the Armed Forces Institute of Pathology in the United States of America, only 23 lesions were diagnosed as CEOTs (which is less than 1% of all OTs). Apparently, just less than 300 cases of CEOT have been reported worldwide (12) and reports on CEOT in Nigeria have been rare. The present study is the first collaborative report on CEOT from five major tertiary hospitals in Nigeria.

The obvious male predilection in our study concurs with previous studies (13, 14) but differs from a Chinese study that reported a female preponderance (14) and a study by Franklin *et al*(12) that reported an equal male / female distribution. Although this gender differences may have been influenced by sample size and ethnic differences, it is may be difficult to identify a consistent trend in gender predilection of CEOT with the small number of published series worldwide. Computed mean age of 31.8 years in the present study, is similar to reported mean ages of 32 and 34 years from previous Chinese and Japanese studies respectively (15,16). This differs from other studies in the English literature where CEOT is reported mostly in the fifth decade of life (12, 14). There could be ethnic / racial differences in the age of occurrence of CEOT but it would be difficult to make definitive conclusions since most reports small case series. Observation from the records in the present study showed that almost all the cases presented as painless slow growing swellings that commonly affected the mandible. CEOT is usually a slow growing painless lesion that sometimes presents with bucco-lingual expansion similar to ameloblastoma. This was observed in three cases in the present study. In addition, five other cases were associated with impacted teeth and clinically mimicked dentigerous cysts. CEOT as well as dentigerous cyst and ameloblastoma, have similar radiographic presentation as unilocular or multilocular defined lesions that mightresult in radiologic diagnostic challenges.

Histologically, CEOT may present with extreme morphologic variations and severe cellular abnormalities mimicking a malignant lesion (16-17). A careful histopathologic examination of CEOT is therefore necessary to avoid erroneous misdiagnosis of amalignant lesion (16). The reddish homogenous hyaline material present in CEOT has been investigated by histochemical, biochemical, immunohistochemicalmethods and electron microscopy (18). It is generally accepted that the homogenous material is amyloid-like, due to positive staining results with Congo red and thioflavine T (5, 6, 12,18). In addition, a report has identified that CEOT associated amyloid consists of a unique protein designated by the authors as Apin (19). Presently there is still no clear-cut agreement on the precise origin of CEOT. Various origins such as reduced enamel epithelium, oral epithelium, stratum intermedium and remnants of dental lamina (1-4, 16) have been postulated. Ai-Ru *et al* (16) stated that under certain conditions the reduced enamel epithelium not only

proliferates in surrounding connective tissue but also undergoes degeneration with eventual formation of calcified corpuscles. They therefore proposed a reduced enamel origin for CEOT.

In the present study, observation of varied radiographic presentations of the tumour was made, and this agrees with reports from scientific literature (16-18,20). Unilocular, non-corticated CEOTs were more frequently observed in the maxilla while multilocular corticated lesions were more frequently observed in the mandible. This radiographic pattern of presentation may be attributed to inherent differences in the bony structure and density of the jaws. CEOT has been associated with impacted teeth which and may be confused with dentigerous cyst on radiograph. The impacted tooth type may however assist in distinguishing between these two lesions, since dentigerous cyst is more frequently associated with impacted 3rd molars while CEOT is more frequently associated with 1st, 2nd molars and premolars (21).

The observed mean duration of lesion of 44.5 month and a mean estimated tumour volume of 471.4 cm3(average monthly volume expansion = 10.59 cm3/month) suggests that CEOT is a relatively slow growing lesion that agrees with previous reports from literature (4, 21). Further studies to determine the true growth rate of CEOT in order to clarify its biology, should however be addressed with larger sample sizes. Although, invasive biologic behaviour of CEOT has been implied to be similar to that of ameloblastoma (16), Krolls and Pindborg (14) concluded that CEOT does not invade as much as ameloblastoma and may therefore be considered a less aggressive lesion.

In conclusion, although categorical conclusions may not be made because of the relative small number of cases, this study showed that CEOT is a rare tumour representing 1.5% of OTs and CEOT seems to present with some subtle geographic/ethnic differences in its demography. However, further studies are required to investigate if these differences are coincidental or genetically determined.

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