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ORIGINAL RESEARCH

Histologic Variants of Calcifying Odontogenic Cyst: A Study of 52 Cases

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ABSTRACT

Aim: This study aimed at evaluating histological features of 52 cases of calcifying odontogenic cyst (COC), which is an uncommon benign odontogenic lesion. The World Health Organization (WHO) classified COC as a neoplasm and used the term calcifying cystic odontogenic tumor (CCOT) for benign cystic type and the dentinogenic ghost cell tumor (DGCT) for the benign solid-type lesions. There is no agreement regarding COC classification.

Materials and methods: A total of 52 cases of COC were selected and reviewed from the archive of the Pathology Department of Taleghani Educational Hospital, Tehran, Iran. To better understand the pathogenesis of COC, the cases were classified.

Results: There were 52 cases (31 males and 21 females). The lesion was found in all age groups, and patients' age from 8 to 61 years. Nineteen cases affected the maxilla, and 33 cases affected the mandible. Except two cases, all were intraosseous lesions. Radiographically, 30 cases showed a unilocular radiolucent area, and 22 cases showed a mixed radiolucent/radiopaque region. Histopathologically, 43 cases were cystic type and 9 cases were neoplastic.

Conclusion: There are two different histopathological entities. In view of these findings, it is very difficult to determine every lesion that has a cystic architecture is truly cystic or is a neoplastic one in nature. It is believed that the solid variants may be neoplastic.

Clinical significance: A better understanding of the histological type of the lesion can provide a classification across patients. This can help in treatment planning to improve patient outcomes.

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INTRODUCTION

Calcifying odontogenic cyst is an uncommon benign odontogenic lesion that was introduced by Gorlin et al[1] for the first time in 1962. The WHO classified COC as a neoplasm and used the term calcifying cystic odontogenic tumor (CCOT) for benign cystic type, the DGCT for the benign solid type lesions which occur centrally or peripherally, and the malignant ghost cell odontogenic carcinoma.[2-5]

The most common histopathological findings include a cystic lesion lined by epithelium with a well-defined basal layer of columnar cells, an overlying layer with many cells resembling stellate reticulum, and masses of ghost epithelial cells that may be in the epithelial cyst lining or in the fibrous capsule. The ghost epithelial cells may become calcified. Dysplastic dentin may be seen adjacent to the basal layer of the epithelium.[6,7] In addition, COC may contain some areas suggestive of neoplasm;[8] however, most of the cases are non-neoplastic.[9] There is no agreement regarding COC classification. In this article, histopathological variants of 52 cases of COC have been discussed.

MATERIALS AND METHODS

A total of 52 cases of COC were selected and reviewed from the archive of the Pathology Department of Taleghani Educational Hospital, Tehran, Iran. For a better understanding of the lesion pathogenesis, the cases were classified as shown in Table 1.

Table 1: Classification of COC

Type I: Cystic type
(A) Simple cyst (nonproliferative)
(B) Proliferative cyst
(C) Ameloblastomatous type
(D) Associated with odontoma
Type II: Neoplastic type
(A) Ameloblastoma ex-COC
(B) Associated with other odontogenic tumors
(C) CDGCT
(D) PDGCT
(E) Malignant COC

CDGCT: Central dentinogenic ghost cell tumor; PDGCT: Peripheral dentinogenic ghost cell tumor

RESULTS

Of 52 cases, 31 were males and 21 were females. The lesion was found in all age groups, and patients' age from 8 to 61 years. The mean age in all cystic variants was 26.2 years. The mean age for patients with neoplastic type was 37.2 years. Nineteen cases affected the maxilla (36.5%), and 33 cases (63.5%) affected the mandible. Except two cases, all were intraosseous lesions. Thirteen cases involved the midline and anterior region. Radiographically, 30 cases showed a unilocular radiolucent area, and 22 cases showed a mixed radiolucent/radiopaque region. Histopathologically, 43 cases (82.7%) were cystic type and 9 cases (17.3%) were neoplastic. The cystic type occurred in four variants: (1) Simple cyst (16 cases; 30.8%), characterized by a simple unicystic structure with a stratified epithelial lining of 4 to 10 cells thick comprising basal columnar or cuboidal polarized cells, and clusters of ghost cells and calcified materials (Fig. 1). Epithelium budding into the connective tissue was found in some cases. In cases of merging the ghost cells to the fibrous cyst wall, cholesterol granuloma was seen. (2) Proliferative type (8 cases; 15.4%), characterized by a relatively thick epithelial-lined cyst with multiple daughter cysts in the cyst wall (Fig. 2). Extensive ghost cell formations, with a marked tendency for calcification, and foreign body reaction to the herniated ghost cells and cholesterol clefts were the other microscopic features for this type. (3) Cystic lesions associated with odontoma (16 cases; 30.8%), with combined features of COC (presence of ghost cells) and odontoma (Fig. 3). (4) Ameloblastomatous type (4 cases; 7.7%), characterized by a unicystic structure lined by unifocal or multifocal intraluminal epithelial proliferation resembling ameloblastoma without Vickers and Gorlin signs along with clusters of ghost cells and calcifications (Fig. 4).

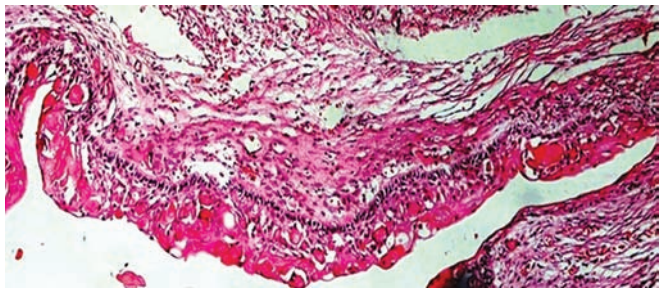


Fig. 1: Higher magnification shows a simple unicystic structure with a stratified epithelial lining and clusters of ghost cells

The neoplastic type occurred in four variants: (1) Ameloblastoma ex-COC or ameloblastoma arising in COC (3 cases; 5.8%), which showed a cystic structure lined by odontogenic epithelium with early ameloblastomatous changes with features suggested by Vickers and Gorlin. Multifocal intraluminal and intramural proliferations showed transformed ameloblastomatous epithelial part. In one case, ameloblastomatous proliferation was in the plexiform pattern (Fig. 5A), and in one case it was in the follicular pattern (Fig. 5B). The transformed

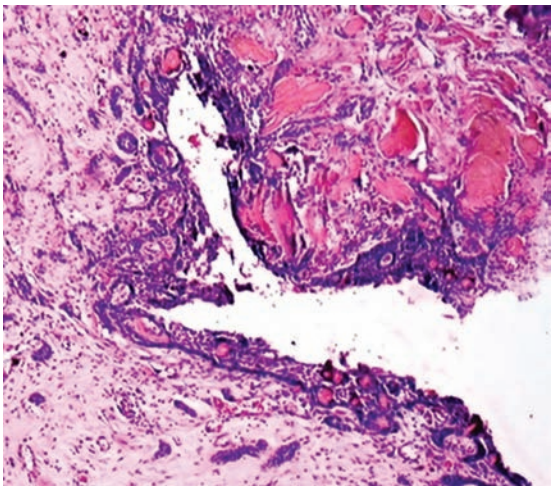


Fig. 2: Low-power view shows proliferative type characterized by epithelial-lined cyst and multiple daughter cysts in the cyst wall. Notice the extensive ghost cell formation

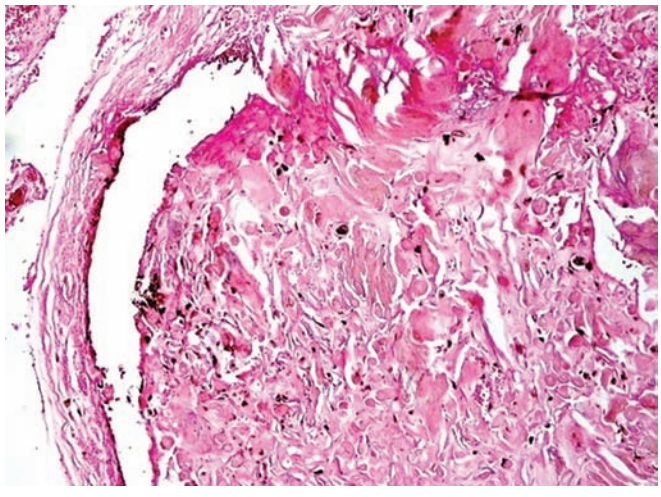


Fig. 3: Lower magnification shows a cystic lesion associated with odontoma. Notice the presence of ghost cells and tooth-like structures

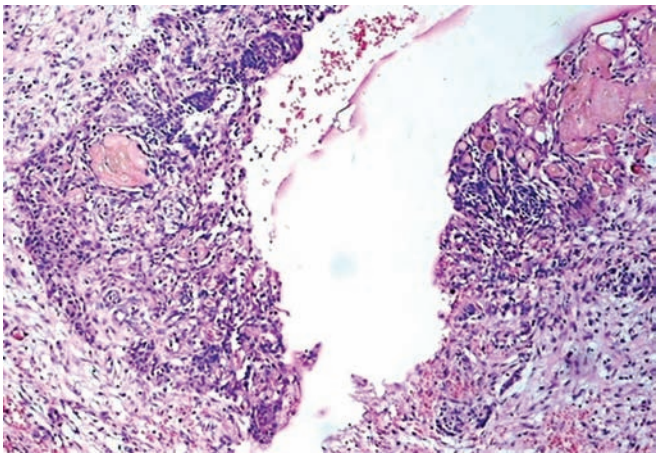
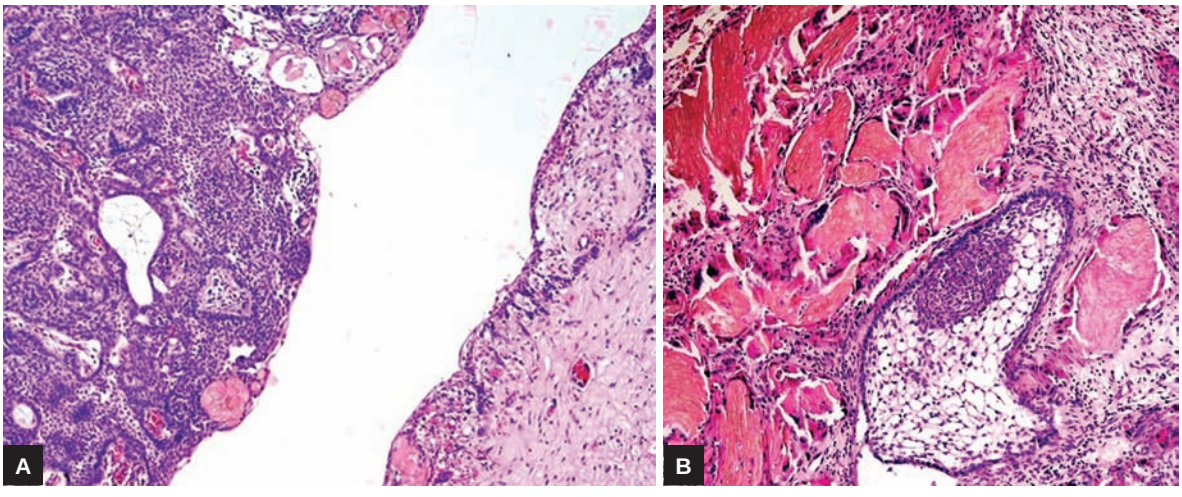


Fig. 4: Medium magnification indicates ameloblastomatous type characterized by a unicystic structure lined by multifocal intraluminal epithelial proliferations along with clusters of ghost cells

ameloblastomatous portion did not contain any ghost cells or calcification, and juxtaepithelial dentinoid was not present. These latter features differentiated the lesion from ameloblastomatous COC. However, several clusters of ghost cells surrounded by foreign body-type giant cell along with calcified materials and dentinoid formation could be seen in the fibrous connective tissue. (2) The COC associated with other odontogenic tumors in two cases [one case of ameloblastic fibroma (Fig. 6) and one case of ameloblastic fibro-odontoma (Fig. 7)]. (3) Central epithelial odontogenic ghost cell tumor (2 cases; 3.8%) which showed cystic epithelium with nests and clusters of transformed ameloblastomatous portions in cyst wall containing ghost cells, calcifications, and dentinoid formation (Fig. 8). (4) Peripheral epithelial odontogenic ghost cell tumor (2 cases; 3.8%), which occurred on the gingiva and resembled peripheral ameloblastoma except for clustered ghost cells in the central portion of follicular islands and the presence of juxtaepithelial dentinoid (Fig. 9). In our series, there was no lesion with malignant changes.[8-10] Table 2 shows the 52 cases of COC.

DISCUSSION

In this study, 52 cases of COC were studied. Among them, 31 cases occurred in males, and 21 cases occurred in females. These findings are in agreement with those of



Figs 5A and B: (A) Lower magnification shows ameloblastoma ex-COC with a cystic structure lined by odontogenic epithelium. Notice the ameloblastomatous changes with plexiform pattern and ghost cells; and (B) Higher magnification shows ameloblastoma ex-COC with a huge amount of ghost cells and ameloblastomatous proliferation in the follicular pattern

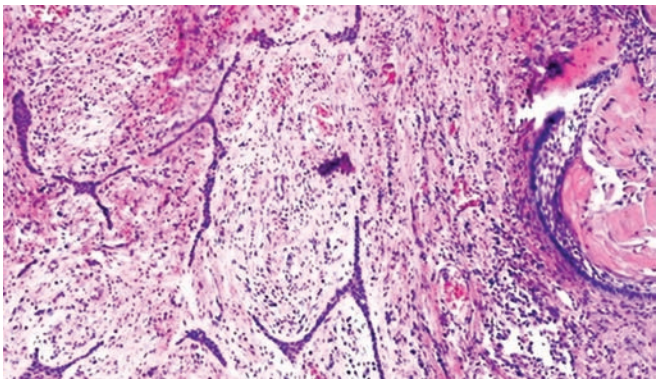


Fig. 6: Lower magnification shows COC associated with ameloblastic fibroma

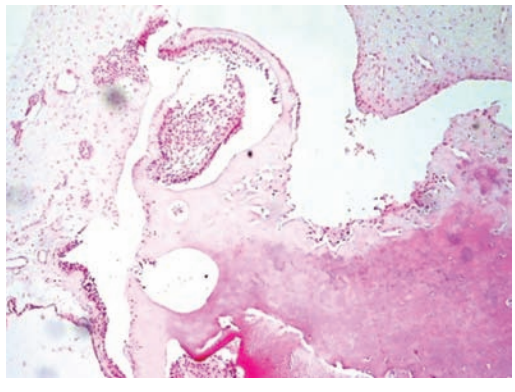


Fig. 7: Lower magnification view of COC with ameloblastic fibro-odontoma

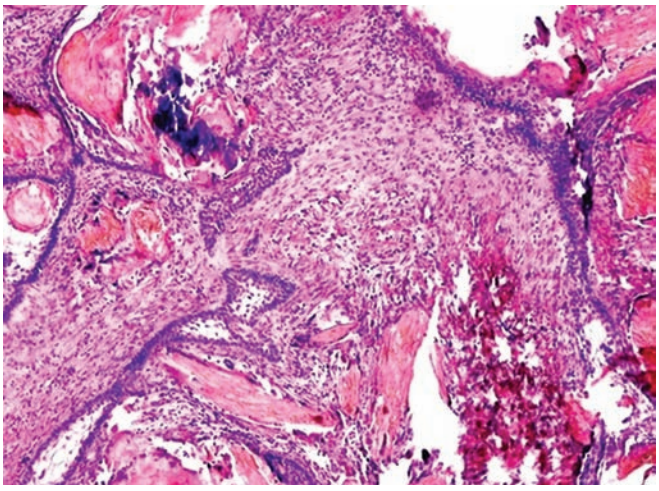


Fig. 8: Lower magnification of central epithelial odontogenic ghost cell tumor which shows a cystic epithelium with nests of transformed ameloblastomatous portions containing ghost cells, calcifications, and dentinoid formation

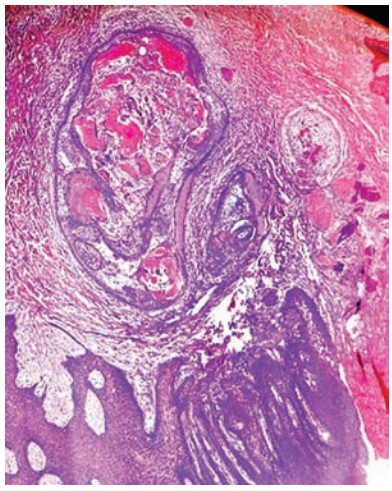


Fig. 9: Lower magnification view shows peripheral epithelial odontogenic ghost cell tumor, with clustered ghost cells and dentinoid materials in the follicular island

Table 2: A demographic profile of 52 patients with COC

Case number	*Gender*	*Age*	*Anatomical site*	*Radiographic findings*	*Histopathologic variant*
1	F	19	Maxillary left canine	Unilocular radiolucent area	Simple cyst
2	F	25	Maxillary right premolars	Unilocular radiolucent area	Simple cyst
3	M	15	Mandibular right premolars	Unilocular radiolucent area	Simple cyst
4	M	29	Mandibular right molars	Unilocular radiolucent area	Simple cyst
5	M	32	Mandibular right molars	Unilocular radiolucent area	Simple cyst
6	F	27	Mandibular right premolars	Unilocular radiolucent area	Simple cyst
7	F	25	Mandibular right molars	Unilocular radiolucent area	Simple cyst
8	M	34	Mandibular right premolars	Unilocular radiolucent area	Simple cyst
9	M	17	Mandibular left premolars	Unilocular radiolucent area	Simple cyst
10	M	26	Maxillary right premolars	Unilocular radiolucent area	Simple cyst
11	M	53	Mandibular right molars	Unilocular radiolucent area	Simple cyst
12	F	22	Mandibular right molars	Unilocular radiolucent area	Simple cyst
13	F	18	Maxillary midline	Unilocular radiolucent area	Simple cyst
14	F	15	Mandibular left premolars	Unilocular radiolucent area	Simple cyst
15	F	19	Mandibular left molars	Unilocular radiolucent area	Simple cyst
16	F	22	Maxillary left incisors	Unilocular radiolucent area	Simple cyst
17	F	45	Mandibular right premolars	Unilocular radiolucent area	Proliferative cyst
18	F	48	Mandibular midline	Unilocular radiolucent area	Proliferative cyst
19	F	28	Maxillary left premolars	Unilocular radiolucent area	Proliferative cyst
20	F	34	Maxillary left premolars	Unilocular radiolucent area	Proliferative cyst
21	M	33	Maxillary right premolars	Unilocular radiolucent area	Proliferative cyst
22	M	20	Maxillary right incisors	Unilocular radiolucent area	Proliferative cyst
23	M	33	Maxillary midline	Unilocular radiolucent area	Proliferative cyst
24	M	25	Mandibular right molars	Unilocular radiolucent area	Proliferative cyst
25	F	19	Mandibular right molars	Mixed radiolucent-radiopaque	Simple cyst associated with odontoma
26	F	9	Maxillary left premolars	Mixed radiolucent-radiopaque	Simple cyst associated with odontoma
27	F	16	Maxillary right canine	Mixed radiolucent-radiopaque	Simple cyst associated with odontoma
28	F	22	Mandibular left premolars	Mixed radiolucent-radiopaque	Simple cyst associated with odontoma
29	M	27	Mandibular right molars	Mixed radiolucent-radiopaque	Simple cyst associated with odontoma
30	M	30	Mandibular right molars	Mixed radiolucent-radiopaque	Simple cyst associated with odontoma
31	M	15	Mandibular left molars	Mixed radiolucent-radiopaque	Simple cyst associated with odontoma
32	M	23	Mandibular right molars	Mixed radiolucent-radiopaque	Simple cyst associated with odontoma
33	M	8	Maxillary left incisors	Mixed radiolucent-radiopaque	Simple cyst associated with odontoma
34	M	27	Mandibular right molars	Mixed radiolucent-radiopaque	Simple cyst associated with odontoma

(Cont'd…)

(Cont'd...)

Case number	Gender	Age	Anatomical site	Radiographic findings	Histopathologic variant
35	M	28	Mandibular right molars	Mixed radiolucent-radiopaque	Simple cyst associated with odontoma
36	M	30	Mandibular right molars	Mixed radiolucent-radiopaque	Simple cyst associated with odontoma
37	M	19	Maxillary midline	Mixed radiolucent-radiopaque	Simple cyst associated with odontoma
38	M	8	Maxillary left incisors	Mixed radiolucent-radiopaque	Simple cyst associated with odontoma
39	F	22	Mandibular right premolars to molars	Mixed radiolucent-radiopaque	Simple cyst associated with odontoma
40	F	30	Maxillary left premolars	Mixed radiolucent-radiopaque	Simple cyst associated with odontoma
41	M	13	Mandibular left premolars	Unilocular radiolucent area	Ameloblastomatous COC
42	M	61	Mandibular left molars	Unilocular radiolucent area	Ameloblastomatous COC
43	M	35	Mandibular left molars	Unilocular radiolucent area	Ameloblastomatous COC
44	F	50	Mandibular right molars	Mixed radiolucent-radiopaque	Ameloblastoma ex COC
45	M	52	Maxillary midline	Mixed radiolucent-radiopaque	Ameloblastoma ex COC
46	F	20	Maxillary left incisors	Mixed radiolucent-radiopaque	Ameloblastoma ex COC
47	M	28	Mandibular left molars	Unilocular radiolucent area	Associated with ameloblastic fibroma
48	M	25	Mandibular left molars	Mixed radiolucent-radiopaque	Associated with ameloblastic fibro-odontoma
49	M	28	Maxillary left incisors	Mixed radiolucent-radiopaque	Odontogenic ghost cell tumor
50	M	25	Mandibular left molars	Mixed radiolucent-radiopaque	Odontogenic ghost cell tumor
51	M	61	Mandibular left premolars	–	Peripheral COC
52	M	59	Mandibular right premolars	–	Peripheral COC

Hong et al[8] study. The cyst can occur at any age; however, most of the cases have been found before age 40.[11] In this study, of the 44 cases, 84.6% of cases occurred before age 40. In this study, only 36.5% of cases were found in the maxilla. However, previous studies had indicated the maxilla and mandible being affected equally.[10,12]

There are two concepts for COC classification. The first concept "the monistic" one classifies all COCs as neoplastic lesions even when they appear as cystic lesions. The second concept "dualistic" classifies all COCs as two entities: cyst and neoplasm.[13] Fejerskov and Krogh[14] supported the dualistic concept. Abrams and Howell believed that due to multipotentiality of odontogenic epithelium, it is expected to see the collision lesions.[13] However, the WHO classified COC as the monistic concept.[15] Calcifying cystic odontogenic tumors can be found centrally (intraosseous) or peripherally (extraosseous); therefore, they are believed to arise from odontogenic epithelial remnants trapped within the jaw bones or gingival tissues.[16] Freedman et al[12] suggested that the tumor cells originate from well-differentiated ameloblasts which have neural crest origin with pluripotential capacity. Praetorius et al[17] and Buchner[10] believed that the reduced enamel organ, or islands of odontogenic epithelium within the tooth follicle, or the remnants of the odontogenic epithelium in the bone or gingival tissue can be the source of the neoplastic cells of CCOT. Altini and Farman[6] suggested the dental lamina rests (rests of Serres) as the origin of COC. The remnants of the dental lamina and surface epithelium have been considered as two major sources for the origin of extraosseous CCOT.[18] The remnants of the dental lamina and surface epithelium have been suggested as the histogenesis of gingival cyst of adults and peripheral ameloblastoma.[19] Ameloblastoma can also be found as both intraosseous lesion (solid or multicystic, and unicystic) and extraosseous (peripheral) lesion. Multicystic/solid type is more aggressive than unicystic and peripheral types.[20] These finding may indicate some similarities between odontogenic lesions, especially ameloblastoma, and some variants of COC which show ameloblastomatous transformation. Ghost cells and calcification, dentinoid formation are other features in COC. Gorlin et al[1] considered them as an inflammatory response. However, Abrams and Howell proposed them as induction of ghost cells in granulation tissue. Ng et al[21] proposed ghost cell as a metaplastic change in the connective tissue without the participation of granulation tissue. Barnes et al[4] explained CCOT as an extremely rare benign cystic neoplasm characterized by an ameloblastoma-like epithelium and ghost cells that have the potential to undergo calcification. The presence of cholesterol clefts in the connective tissue may be a proof for foreign body reaction in the cyst wall. Epithelial budding and migration of ghost cells from epithelial lining also occur in COC.[8,10] Coexistence of COCs with other odontogenic lesions has been reported, which raises the question whether these features are secondary phenomena in preexisting COCs or the COCs develop secondarily in preexisting other odontogenic lesions;[22] however, several investigations believed that proliferating epithelial odontogenic islands may induce the mesenchymal tissue to develop

other odontogenic tumors.[23-25] Ameloblastomatous COC is different from true ameloblastoma arising in COC as despite ameloblastoma ex-COC, the ghost cells and dystrophic calcification can be observed within the proliferative epithelium. The coexistence of COC with odontoma is controversial. While some studies suggest that COC develops secondarily from odontogenic epithelium which forms the odontoma, others believe that as odontogenic epithelium has the potential for mesenchymal induction, the odontoma develops secondarily from the lining epithelium of the COC. The latter concept can explain the coexistence of some other odontogenic tumors, such as ameloblastic fibro-odontoma and ameloblastic fibroma with COCs, even though this concept can explain the dentin formation in COCs.[8,17,22,26] Another lesion is DGCT.[27] Some odontogenic lesions include calcifying epithelial odontogenic tumor, ameloblastic fibro-odontoma, and adenomatoid odontogenic tumor. For the lesions with little or no mineralization, dentigerous cyst can be considered in differential diagnosis of CCOT.[10,28] Surgical enucleation, curettage, and marsupialization are the selected treatment approaches, but the ameloblastomatous CCOT should be treated like an ameloblastoma.[29]

CONCLUSION

There are two different histopathological entities. One is defined by the presence of a cystic lesion, and the other is an infiltrative lesion with some degree of odontogenic epithelium islands and varying masses of ghost cells and dentinoid materials in the stroma. In view of these findings, it is very difficult to determine every lesion that has a cystic architecture is truly cystic or is a neoplastic one in nature. It is believed that the solid variants may be neoplastic.

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