Calcifying odontogenic cyst

Range, variations and neoplastic potential

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16 cases of calcifying odontogenic cysts (C.O.C.) were studied and reevaluated. It could be concluded, that the group contained two entities, a cyst and a neoplasm. The cyst occurs as three variants. 1. A simple unilocular cyst with moderate mural proliferations of epithelium and no, or sparse amounts of, dentinoid (dysplastic dentin); it seems to occur during man's entire life span. 2. A unilocular cyst which produces compound or complex odontomes in its luminal part, more rarely it may instead produce an intramurally growing ameloblastic fibroma, which may call for more radical surgery. It occurs mainly in patients between 10 and 29 years of age. 3. A unilocular cyst with extensive luminal as well as mural ameloblastomalike proliferations of epithelium. The C.O.C. may be located outside or inside the bone according to the location of the source of odontogenic epithelium, from which it develops.

The neoplasm shows an entirely different structure. It consists of ameloblastoma-like strands and islands of odontogenic epithelium growing infiltratively in a mature connective tissue. Varying amounts of ghost cells are seen in the epithelium and varying amounts of dentinoid is formed in contact with the odontogenic epithelium. The term «Dentinogenic ghost cell tumour» is suggested for this lesion. It is possible that it occurs predominantly in the later part of life. It occurs as an extraosseous as well as an intraosseous lesion. Recurrence has been observed following cystectomy.

Key-words: Odontogenic tumors, odontomes, ghost cells, dentinoid

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When the term «Calcifying Odontogenic Cyst» (C.O.C. in the following) was coined by Gorlin, Pindborg, Clausen & Vickers, 1962 (12), to describe a new entity, the cystic nature of the lesion was stressed as well as its peculiar histological features and pathogenesis.

Later, it became evident that the nature of the lesion was more varied, and in the international histological classification of odontogenic tumors issued by W.H.O. in 1971 (20) it was indicated that the cyst may be associated with a complex odontoma or with tissue resembling an ameloblastic fibro-odontoma. The definition given was as fol-

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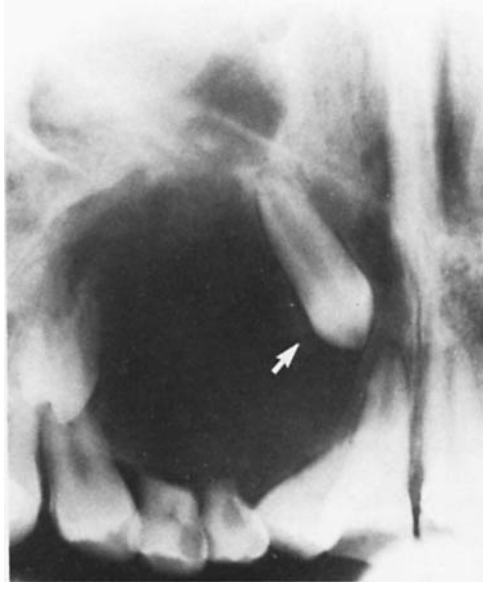

Fig. 1. Radiogram of the right side of the maxilla of a 13 year-old boy showing a cystic lesion measuring 5 x 4 cm (case 6). The cyst is not an ordinary dentigerous cyst. Preservation of a thin lamella of cortical bone from apex of the root till the point indicated by the white arrow can clearly be seen on the original radiogram. The lesion has probably developed from a minor part of the reduced enamel epithelium.

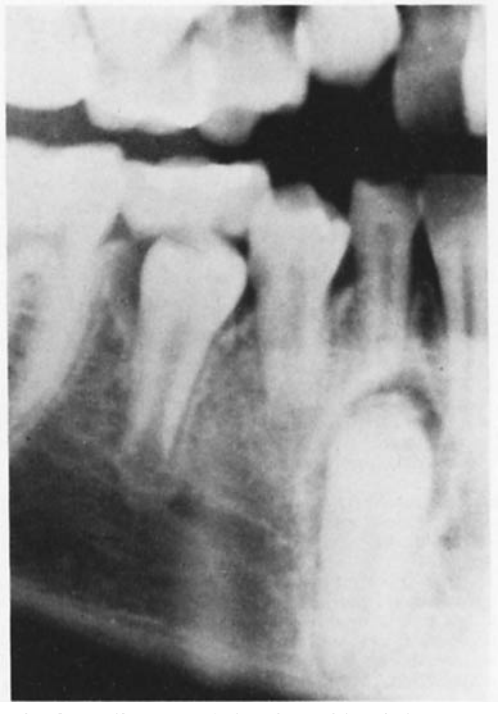

Fig. 2. Radiogram of the right side of the mandible showing a radiolucent area containing radiopaque spots around the tip of the crown of 43. The patient is an 11 year-old boy (case 3).

lows: «A non-neoplastic cystic lesion in which the epithelial lining shows a well-defined basal layer of columnar cells, an overlying layer that is often many cells thick and that may resemble 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 dentine may be laid down next to the basal layer of the epithelium.»

The presence of the so-called «ghost cells», which are assumed to represent an abnormal type of keratinization (3, 8, 14, 18, 27, 28) with affinity for calcification (22, 24) is the most conspicuous feature of the lesion. The mere presence of «ghost» cells in a lesion, however, does by no means justify it being diagnosed as a C.O.C. A number of different lesions show formation of ghost cells. In craniopharyngiomas they were found as early as 1904 by Erdheim (5). Among lesions occurring in the jaws they have been described in ameloblastic fibro-odontomas (19) and complex and compound odontomas (9,15,17, 19,23). Furthermore, the present authors have observed them in ameloblastomas and carcinomas.

Hence, the diagnosis C.O.C. should only be used for a lesion in which the formation of ghost cells takes place in a typical epithelial cyst lining presenting a well defined basal cell layer of cuboid or short cylindrical cells and an overlying layer consisting of cells that bear a striking resemblance to the stellate reticulum-like cells in ameloblastomas. Most often, however, the typical changes occur in one or several focal areas of the cyst with interjacent areas covered by a few cells thick layer of un-

Table 1. *Clinical and radiologic features of 16 cases of calcifying odontolgenic cyst. Tooth designation is in accordance with W.H.O.*

Case Identification	Age	Sex	Location	Extra/intra-osseous	Symptoms	Radiology	Type of operation
1 42.990	1	M	84	Extra	Bluish swelling covering unerupted 84	(eruption)	Marsupialisation
2 18.530	11	M	13	Intra	Bony hard swelling in region of 13	As a follicular cyst of unerupted 13	Cystectomy
3 61.385	11	M	33	Intra	–	As a follicular cyst of unerupted 33	Cystectomy
4 066 – D1030	12	F	22, 23	Extra	Firm swelling 6 x 6 mm of palatal mucosa	–	Extirpation
5 074 – D675	12	M	right maxilla	Intra	Bone swelling	–	–
6 47.413	13	M	13	Intra	Bony swelling of premolar incisor region	As follicular cyst at 13, measuring 5 x 4 cm	Cystotomy followed by cystectomy 4 months later
7 15.429	17	M	33 to 38	Intra	Bony swelling of premolar molar region	As follicular cyst of 35, 36, 37, 38	Resection
8 61.041	23	F	33, 34	Intra	–	Cystic radiolucency between 33, 34	Cystectomy
9 14.000	32	F	33, 34	Intra	Bony swelling in region of 33,34	Cystic radiolucency between 33,34. Resorption of adjacent roots	Cystectomy
10 35/63	41	F	31, 32	Extra with erosion of bone	Swelling in region of 31,32	Cystic radiolucency between roots of 31,32. Resorption of roots	Cystectomy
11 068-D10	47	M	48, 47	Intra	–	Cystic radiolucency from 48 to 46, from base of mandible. Resorption of roots of adjacent teeth	Cystectomy
12 48.889	52	M	22, 23	Extra with erosion of bone	Swelling of palatal mucosa og rerio 22,23	Cystic radiolucency with resorption of adjacent teeth	Cystectomy
13 173/61	57	M	25 → 28	Intra	–	Cystic radiolucency in edentulous area	Cystectomy of cyst bearing area
14 2014/52	363	F	48	Intra	Sore swelling of covering mucosa	Cystic radiolucency in 48 area – edentulous	Cystectomy followed two years later by a resection due to recurrence
15 42.358	76	M	44, 45	Intra	Swelling of edentulous area	Cystic radiolucency in edentulous area	Cystectomy
16 47.804	78	M	46, 47, 48	Intra	Slow growing swelling over months	Cystic radiolucency	Cystectomy

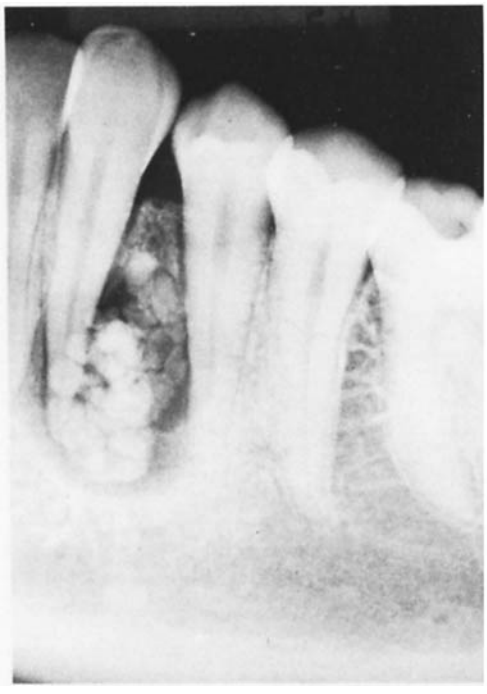

Fig. 3. Radiogram of the left side of the mandible of a 23 year-old woman with a unilocular cystic radiolucency between the roots of 33 and 34 filled with small radiopaque bodies (case 8).

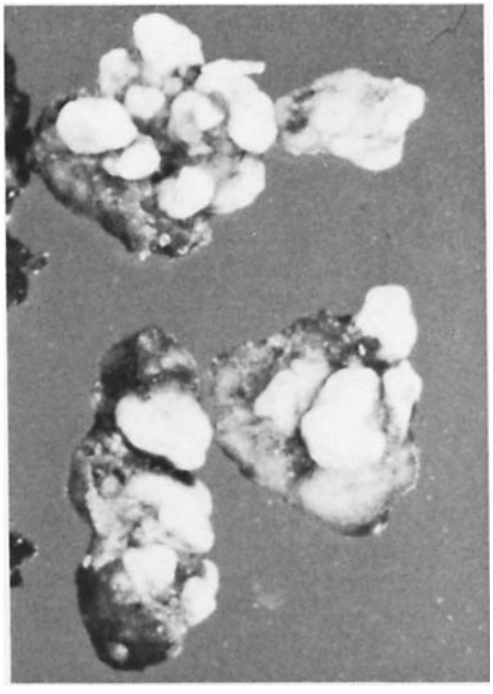

Fig. 4. Macroscopic photo of part of the lesion shown in Fig. 3. Numerous odontoids are developed from the cystic membrane with the «crowns» pointing towards the lumen (case 8).

keratinized squamous cell epithelium. Probably because of the ameloblastomatous resemblance, Boss 1959 (2) and Spirgi 1960 (26) published typical cases of C.O.C. as ameloblastomas before the term C.O.C. was coined.

The purpose of the present paper is to evaluate the range, variations and neoplastic potential of the C.O.C. based on a study of 16 cases that fulfilled the criteria given in the histological classification issued by W.H.O.

MATERIAL AND METHODS

The material consisted of 16 patients, in which the diagnosis of a calcifying odontogenic cyst had been made in the Department of Oral Pathology of the Royal Dental College of Copenhagen and the Department of Oral Pathology and Genetics, School of Dentistry, University of Minnesota. The age varied from 1–78 years and 11 males and 5 females comprised the material. Two of the lesions were extraosseous with no bony involvement, two were extraosseous but with erosion of the underlying bone, and the remaining 12 cases were all intraosseous but with a varying degree of destruction of the overlying bone. In Table 1 the clinical characteristics are presented; however, these features will be dealt with in detail in a following publication. As indicated in Table 2 and 3, some of the cases have been published earlier in another context.

Serial sections stained with Hematoxylin-eosin, Goldner staining method, Masson's thrichrome, and van Gieson connective tissue stain were analyzed in most cases, in some cases only few sections were available. The

Table 2.

	Epithelium	Ghost cells	Dental hard tissue
Type 1A Case 1– 1 year Case 6–13 year Case 10–47 year Case 13–57 year* Case 15–76 year Case 16–78 year	A nonkeratinized cyst epithelium, mostly thin with focal appearance of stellate reticulum–like areas within the cyst epithelium; in these areas palisading was characteristic. Varying amounts of islands and strands in underlying connective tissue.	Within the epithelial wall and occasionally as islands in the underlying connective tissue. Varying degree of calcification.	None to sparse amount of dentinoid in the connective tissue in areas in contact with the epithelium.
* This case has previously been published as case no. 11 by Gorlin et al. 1962 (12)			
Type 1B Case 2–11 year Case 3–11 year Case 4–12 year Case 5–12 year Case 7–12 year Case 9–23 year Case 9–32 year*	As 1A, but budding of the basal cells and islands and strands of odontogenic epithelium were present in the connective tissue cyst wall. Marked luminal proliferation of the ghost cell containing epithelium.	Numerous ghost cells mainly in the islands of the luminal proliferations but also found in cyst epithelium and in connective tissue.	From a few to numerous tooth-like structures as in a composite odontome. The odontoids are arranged with a parallel projection of the crowns towards the lumen and the pulps towards the fibrous capsule. Vast amount of dentinoid mainly intermingled with the luminal projections from the cyst wall. In one case only one malformed tooth was present (Case 9)
* This case has previously been published as case no. 10 by Gorlin et al. 1962 (12)			
Type 1 C Case 11–47 year	As 1 B, but with vivid ameloblastomatous proliferation, luminal as well as mural.	As 1 A	Vivid formation of dentinoid in relation to islands of epithelium.

following characteristics of the C.O.C. were used to describe the specimens:

Ghost cells: pale eosinophilic swollen epithelial cells that have lost the nucleus but show a faint outline of the cellular and the nuclear membrane. They contain many tonofibrils.

Stellate reticulum: stellate epithelial cells joined by cytoplasmic prolongations and orientated with wide intercellular gaps. In normal tooth development they make up the central part of the enamel organ.

Dentinoid: osteoid-like atypical, dysplastic dentin that develops in direct relationship to odontogenic epithelium. Dentinoid contains cells and collagen, the normal tubular structure of dentin is absent.

Palisading: an accentuation of the basal cell layer of the epithelium with a linear arrangement of the centrally located nuclei which has an increased basophilia.

Polarisation: an excentric location of the nuclei of the basal cell layer with the nucleus located in the part of the cell most distant from the basement membrane.

Budding: formation of epithelial buds from the basal cell layer extending into the adjacent connective tissue.

Luminal proliferation: Proliferation of the lining epithelium into the cystic cavity.

Mural proliferation: proliferation of the lining epithelium into the fibrous capsule.

RESULTS

Two major types of the C.O.C. which differed markedly in many respects were disclosed. Type 1 is a unicystic process, where the lesion seems to develop either from the reduced enamel organ or from islands or remnants of odontogenic epithelium within the follicle, the gingival tissue, or the bone. Fig. 2 is an example of a cyst developed from a very localized area of the reduced enamel organ from the tooth follicle surrounding an impacted canine in the lower right jaw.

In Table 2 the histological characteristics of the unicystic type is tabulated, three sub-groups could be identified.

Type 1A, the simple unicystic type, in most cases contained a sparse amount of dentinoid, otherwise no dental hard tissues were formed. The major portions of the lining cyst epithelium was of a low two-three layer thick cuboidal or squamous epithelium. The appearance of the stellate reticulum and ghost cells was focal (Fig. 6). Four of the six patients were more than 45 years old.

With regard to type 1 B, the odontome producing type, it was characteristic that all the dental hard tissues were situated in close relation to the luminal part of the lining cyst epithelium. Odontome like formations were only formed when the dentinoid was present within the lumen of the cyst indicating disruption of the basement membrane of the lining epithelium. The tooth like structures projected from the periphery with the embryonal pulp tissue situated upon the fibrous capsules and the

Table 3.

	Epithelium	Ghost cells	Dental hard tissues
Case 12–52 year Case 14–63 year*	The epithelium is present as numerous ameloblastomatous-like proliferations in a fibrous connective tissue. Cysts develop within some of the individual islands. Many islands with a stellate reticulum-like arrangement do show polarisation of the basal cell layers.	Varying amount of ghost cells within the epithelial islands, few in the connective tissue, and only when disintegration of the basement membrane is present.	Varying amount of dentinoid is seen in intimate contact with epithelium, where disruption of basement membrane is present.

* This case has previously been published as case no. 11 by Husted & Pindborg, 1953 (13) and as case no. 12 by Gorlin et al. 1962 (12)

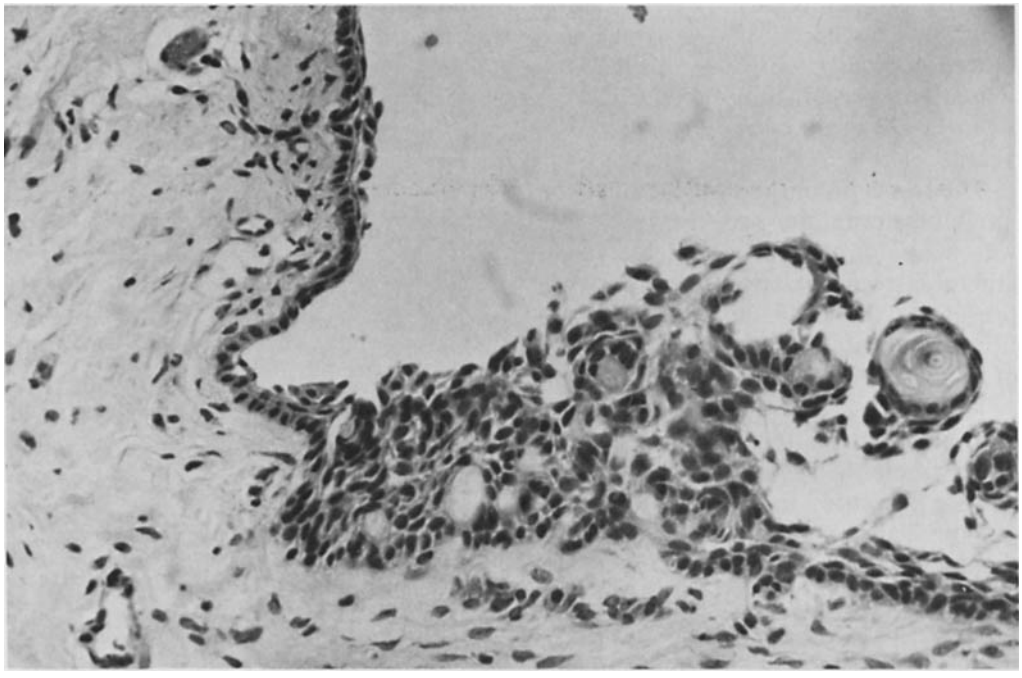

Fig. 5. Photomicrograph of part of the wall of a C.O.C. in an 11 year-old boy (case 3). There is a sharp limit between the reduced enamel epithelium to the left and the proliferating cyst epithelium to the right. H.-E. X 80

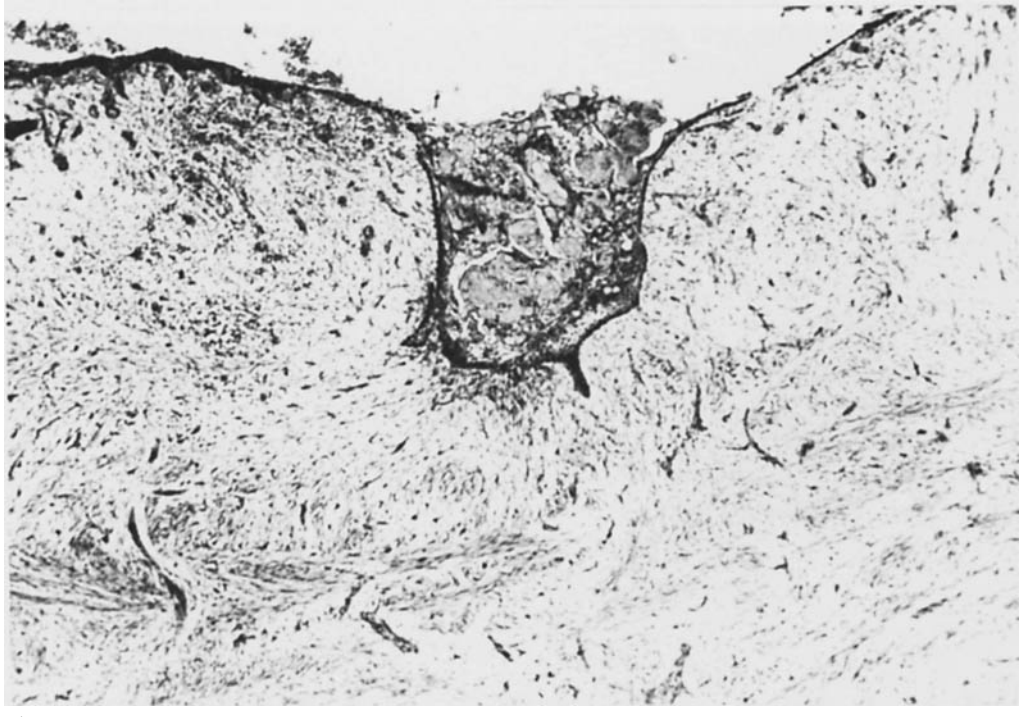

Fig. 6. Cystic lining of a simple unicystic C.O.C. (case 13). In the center a focal appearance of stellate reticulum-like cells and ghost cell is seen. To the sides a thin squamous cell epithelium. H.-E. X 51.

crowns projecting towards the center (Fig. 8). This could also be visualized macroscopically (Fig. 4). Seven patients comprised this type, all were from 11–32 years of age, five below 20 years.

The last type in the cystic group, the ameloblastomatous proliferating type, was seen in only one patient. Here, ameloblastoma-like proliferations were present in the connective tissue of the fibrous capsule as well as in the lumen of the cyst (Fig. 10).

The Type 2 is a neoplastic process with a growth pattern resembling that of an ameloblastoma. The characteristics are presented in Table 3.

Type 2 shows a completely different picture in comparison with type 1. Although many of the characteristic features of the C.O.C. are present, the lesion appears to be a neoplastic process with a histological pattern similar to that of an ameloblastoma and not as an unicystic lesion. Both patients were elderly, 52 and 63 years of age, in contrast to the unicystic odontome producing type (1B), which predominantly occurs in younger age groups.

DISCUSSION

The varied histological picture of C.O.C., which was realized already when the entity was first described by Gorlin et al. 1962 (12) and by Gold 1963 (11) has created an increasing discontent with the inappropriate name of the lesion during more recent years. Several authors have expressed the opinion that not all the variations observed can easily be accepted as falling within the range of the C.O.C., (1, 4, 7, 8, 10, 16, 21, 25).

In the present study of 16 cases originally diagnosed as C.O.C. four different patterns could be distinguished. Three of these which we have named

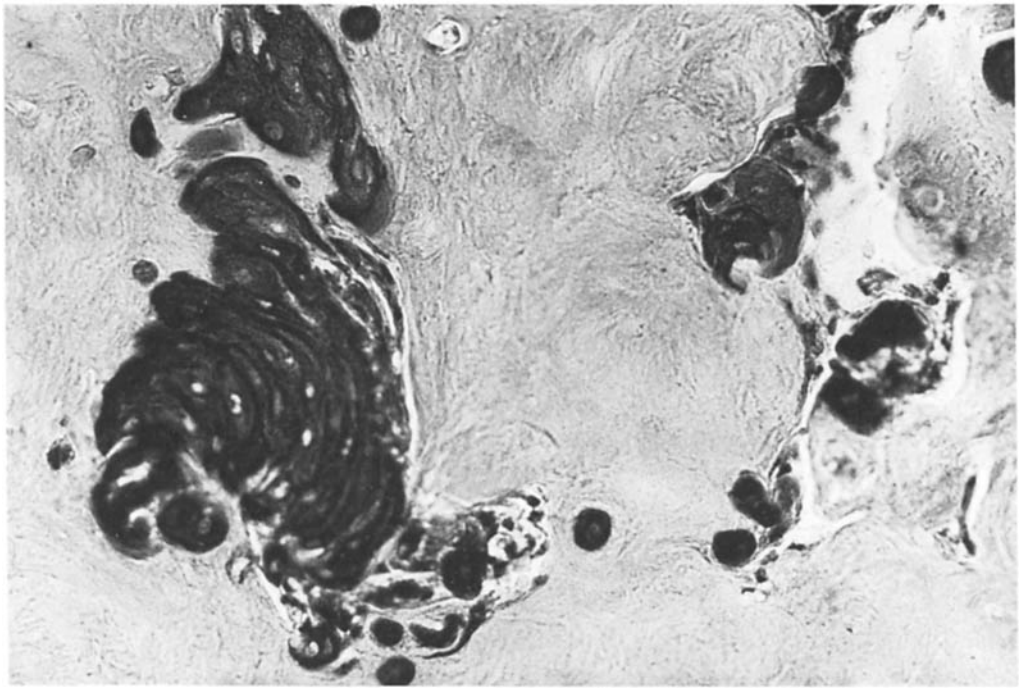

Fig. 7. Ghost cells embedded in dentinoid (case 2). The two types of tissue are both eosinophilic, but separate very clearly in the van Gieson stain. X 80.

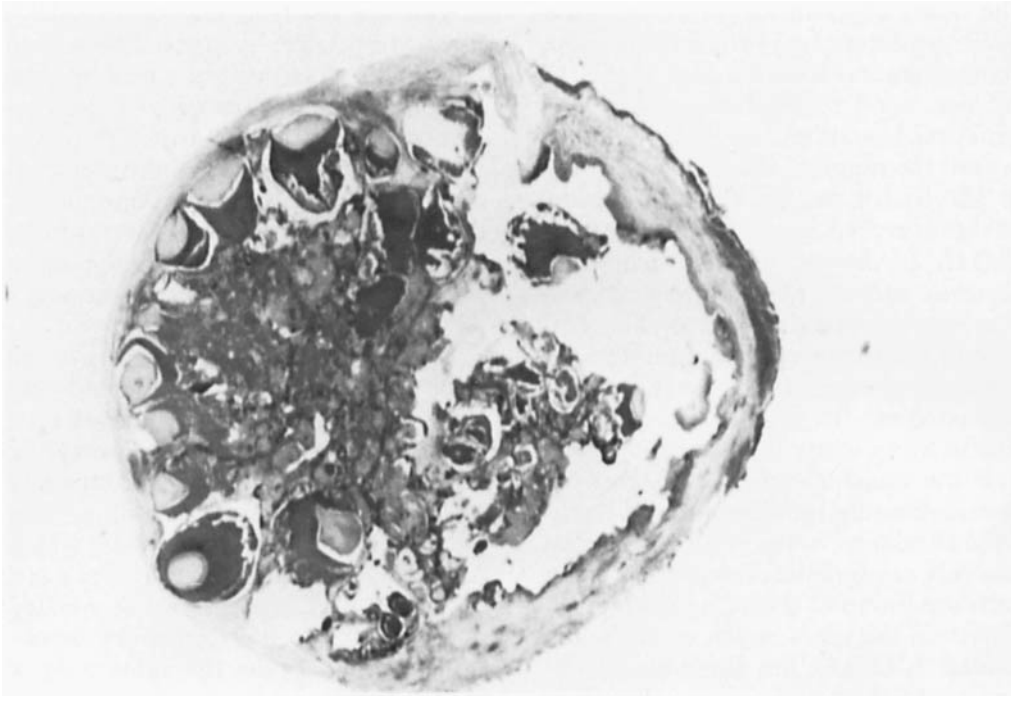

Fig. 8. Low power magnification of an odontome-producing C.O.C. in an 11 year-old boy (case 2). The odontoids are formed in the cystic capsule with their crowns projecting towards the center. Van Gieson stain, X 6.

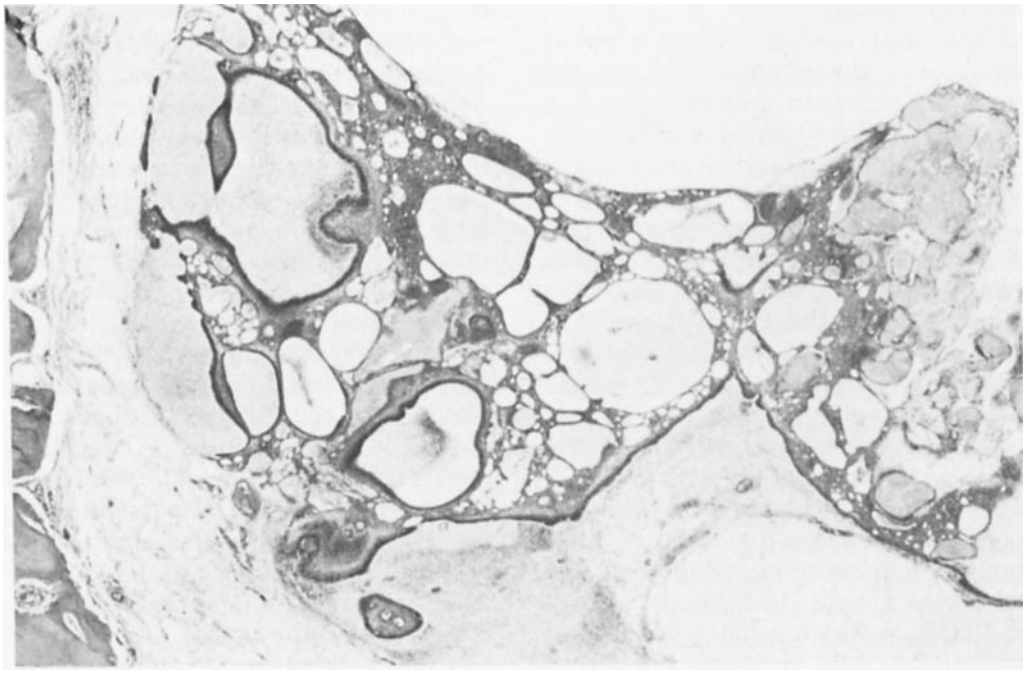

Fig. 9. Section of the wall of an ameloblastic fibroma-producing C.O.C. in the mandible of a 17 year-old boy (case 7). Proliferation of odontogenic epithelium is seen. To the left it borders areas of embryonic pulp tissue. To the right formation of ghost cells and dentinoid is seen. H.-E. X 32.

the *simple unicystic type* (1A), the *odontome producing type* (1B) and the *ameloblastomatous proliferating type* (1C) all presented themselves primarily as unicystic lesions and could be accepted within the range of the C.O.C.

The fourth pattern was too unusual to be accepted as a variation of the C.O.C. It showed definite neoplastic features and the development of cysts was only observed as a secondary feature in islands of epithelial tumour tissue analogous to what is seen in ameloblastomas. The lesion should be separated as an entity of its own. We suggest the name *Dentinogenic ghost cell tumour* because the formation of dentinoid in relation to the epithelial islands is a very conspicuous feature and ghost cells are found to a varying degree.

Within the types which could be accepted as C.O.C. the ameloblastomatous proliferating cyst was only represented by a single case (No. 11), which makes it impossible to draw any general conclusions.

The simple unicystic type (1 A) seems to occur at almost any age of life, the youngest being an eruption cyst in a one year old boy and the oldest presenting itself as a «residual cyst» in a 78 year old man.

The odontome producing type (1 B) occurred mainly in the age group between 10 and 19 years, but a single case which showed the development of a malformed tooth in the place of a missing 34 occurred in a 32 year old female patient, i.e. at an age where normal odontogenesis has ceased. In the remaining six cases of this type, four (2, 3, 5, 8) showed formation of hard dental tissues similar to that found in compound and complex odontomes. In case No. 4 only sparse material was available in which tubular dentin and pulp tissue could be found, but no enamel.

In one case (No. 7) extensive proliferations of tissue similar to an ameloblastic fibroma (Fig. 9) could be seen to proliferate from the cystic wall into the surrounding bone causing a destruction of the mandible from 33 to the angle. No tubular dentin or enamel could be found but vast amounts of dentinoid which, however, seems to be a product of the cystic part of the lesion and not of the apparently secondary developed odontogenic tumour.

In none of the cases belonging to the odontome producing type could any signs of simultaneous appearance of two separate pathological processes be found, e.g. a calcifying odontogenic cyst and a composite odontome. Neither did we get the impression which Altini & Farman 1975 (1) expressed that the C.O.C. represents a secondary phenomenon occurring within a preexisting lesion. To us the odontome is clearly developed in the cystic wall, as it appears from Fig. 4 and Fig. 8. Shear 1976 (25) also raised the question whether those calcifying odontogenic cysts which have other features of odontogenic tumours develop these secondarily, or whether they are themselves secondary phenomena in pre-existing odontogenic tumours. In the present material we found substantial evidence that what appears to be an odontogenic tumour simply is an integrate part of the entire lesion and is developed from the wall of the C.O.C.

Regarding the treatment of these lesions it has to be the tumourous part that determines the type of operation. Although in the presence of an odontome extirpation will still be adequate, the mural development of an ameloblastic fibroma may require a more radical procedure.

Altini & Farman 1975 (1) considered at least four of their cases, and possibly a further 13 from the literature, to have a dentigerous relationship with unerupted teeth, and found areas of lining re-

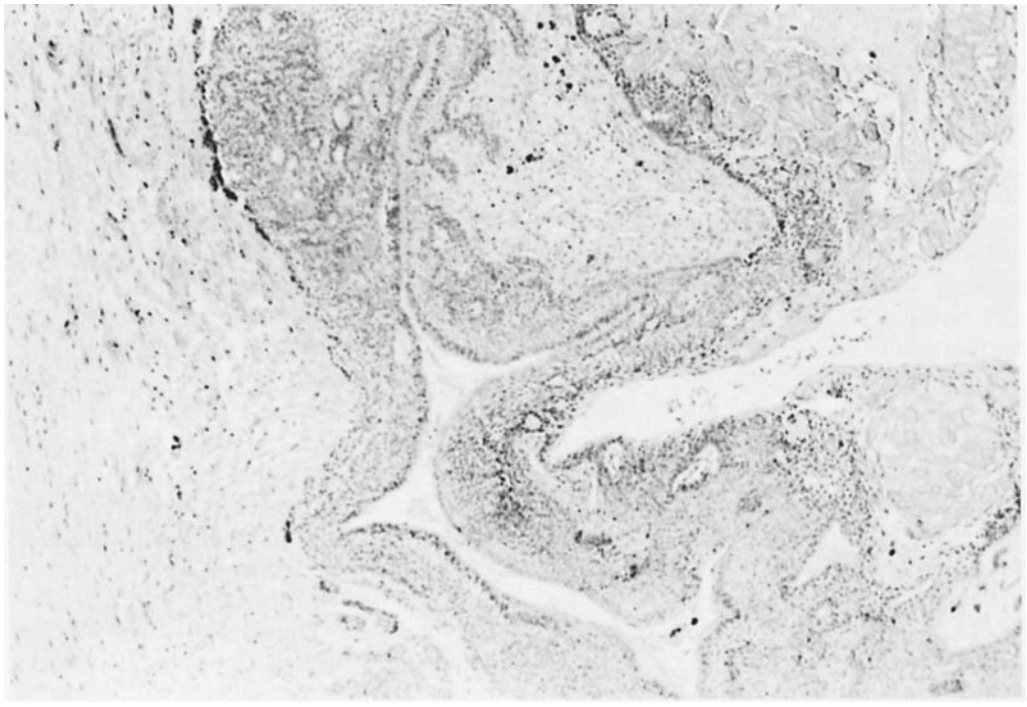

Fig. 10. Section from part of the cystic wall in a C.O.C. with ameloblastomatous proliferations occurring in a 47 year-old man (case 11). The lesion forms ghost cells and dentinoid, but no embryonic pulp tissue can be found. H.-E.X 80.

sembling reduced enamel epithelium in six of eight cysts, that they described. Apart from the eruption cyst, three cases in the present series showed the development of the C.O.C. in close relation to the crown of an embedded tooth. From the radiographs of two of them (Figs. 1 and 2) it can be seen that no follicular cyst has developed. The cortical bone surrounding the follicle of the tooth is intact apart from a minor area in which the C.O.C. seems to have developed and grown out laterally. This radiographic observation is supported by the finding in one of the cases (3) of a very abrupt change of the reduced enamel epithelium into the epithelial lining of a C.O.C., Fig. 5. This bears resemblance to other lesions that are supposed to arise from changes in a single or a few cells like the sharp limit found between normal and dysplastic epithelium in e.g. leukoplakia or erythroplakia.

In three of the cases (9, 10, 11) the C.O.C. causes resorption of the root of an adjacent tooth. In several cases, however, the C.O.C. developed in edentulous areas, hence the limited material does not permit any further conclusions regarding the ability of the cyst to resorb adjacent teeth.

Most of the cysts in the present series were intraosseous, although several of them showed resorption rather than expansion of the cortical plate, thus creating a direct contact between the cyst wall and the oral mucosa. Besides the eruption cyst (case 1) two other C.O.C. developed outside the bone (case 4 and 10); the latter showed saucerisation of the adjacent bone. Whether the C.O.C. develops as an extraosseous or an intraosseous cyst seems only to depend

on the location of the odontogenic epithelium which constitutes the source of the lesion. It does not seem to have any relation to the behaviour or histological features of the cyst.

As mentioned above, two of the cases in the series studied could not be regarded as C.O.C. but must be considered as neoplasms, for which we suggest the name *Dentinogenic ghost cell tumour*. One of them (case 12) developed in the gingiva of the maxilla of a 52 year-old male, the other one (case 14) occurred in an edentulous area of the mandible of a 63 year-old female. The first was operated on at a very early stage, the second showed recurrence two years after currettage and was then treated with jaw resection. In the set of microscope slides used by the W.H.O. International Reference Centers for histological typing of odontogenic tumours two similar cases were incorporated, one occurring in a 72 year-old female, and the other one in a 53 year-old male. The latter showed recurrence. A similar case was recently published (29).

In his book «Cysts of the oral regions» Shear 1976 (25) presents a histogram showing the age distribution of 70 patients with C.O.C. The histogram shows two peaks, one at the age period 10–19 years, and another (which is about 50 % lower) at the age period 60–69 years. In the age group 40–49 years there are almost no patients. Very few diseases show such a double-peak age distribution, so this distribution per se makes it highly suspicious, that we are dealing with at least two different entities.

The odontome producing type (1 B) of C.O.C. in the present series (Figs. 3, 4, 8) certainly shows a tendency to occur at an age period corresponding to the 10–19 years' peak. The dentinogenic ghost cell tumour (Figs. 11, 12) possibly shows a tendency to occur around the later age peak (50 – 79 years) while the simple unicystic C.O.C. (Fig. 1, 6) probably occurs more evenly throughout the life span. These problems will be further clarified in a following study of the cases of C.O.C. published in the literature.

Recently, Donath et al. 1979 (4) advocated that dentinoid or dysplastic dentin is not a product of mesodermal cells, but represents a hard type of keratin similar to that found in nails. They based their opinion on the study of H–E stained paraffin sections and ultrathin sections studied in light and electron microscope. They only found ultrastructural evidence of collagenous fibres in dentinoid in areas in immediate vicinity of fibroblasts. We cannot support this opinion. Although we did not make any ultrastructural studies and admitting that dentinoid is always produced in close contact with odontogenic epithelium, we consider two findings indicative of a mesodermal origin of the material. One is that dentinoid stained with connective tissue stainings like van Gieson, Heidenhain, Goldner and Masson always stains like collagen, and the other finding is that dentinoid was never found in the luminal proliferations unless there was a disintegration of the basement membrane with outgrowth of connective tissue between the epithelial ghost cells. Furthermore, it could be observed in the odontome producing type of the C.O.C. that fusion may take place between dentinoid and tubular dentin, the former being delineated by fibroblast-like cells, the latter by odontoblasts developed from dental pulp tissue.

It should be pointed out that the dentionoid is only studied with difficulty in H–E stained sections, since it is eosinophilic like most other structures surrounding it. Only by means of connective tissue staining procedures like van

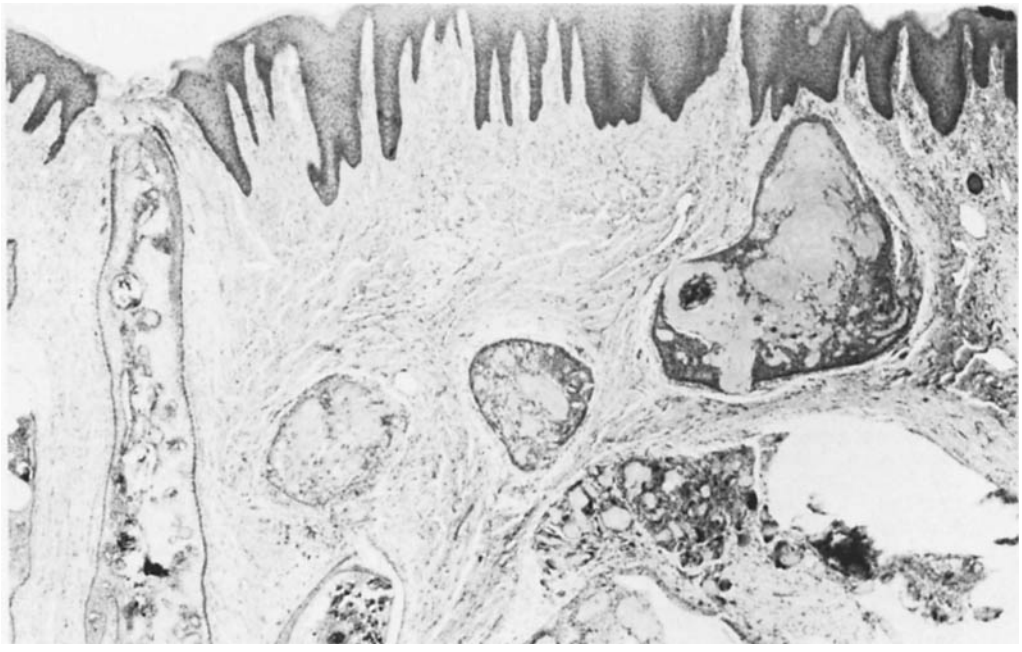

Fig. 11. Section of a peripheral dentinogenic ghost cell tumour (D.G.C.T.) in the maxilla of a 52 year-old man (case 12). In a fibrous connective tissue below the surface epithelium tumour islands of odontogenic epithelium are seen. They contain ghost cells and in areas with disintegration of the basement membrane dentinoid is formed in contact with the epithelium. H.-E. X 32.

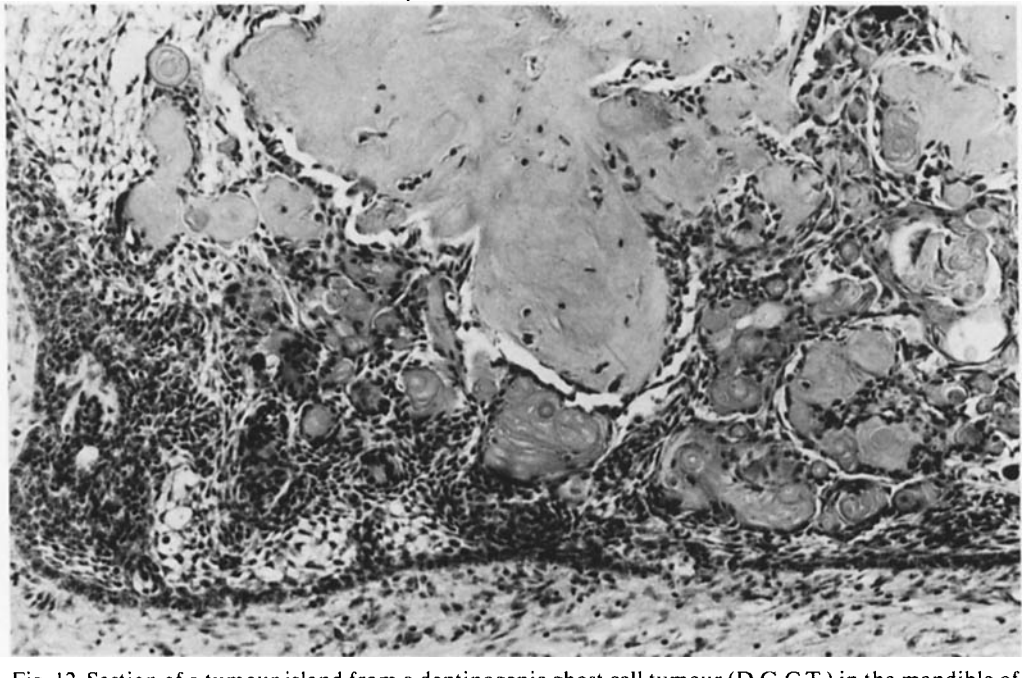

Fig. 12. Section of a tumour island from a dentinogenic ghost cell tumour (D.G.C.T.) in the mandible of a 63 year-old woman (case 14). Stellate reticulum-like cells and ghost cells are seen as well as dentinoid formed in contact with epithelial cells by connective tissue cells penetrating the island from areas (not seen in the figure) where the basement membrane is disintegrated. H.-E. X 125.

Gieson, Heidenhain, Goldner or Masson is it possible to distinguish the ectodermal parts from the mesodermal parts of the sections (Fig. 7).

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