

The Early History of Odontogenic Ghost Cell Lesions: From Thoma to Gorlin

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Abstract To reappraise the early history of odontogenic ghost cell lesions (OGCL), the extensive world literature published from 1838 to 1962 was reviewed. In light of the long history of OGCL, the term “calcifying epithelioma of Malherbe” first appeared in a 1931 French report, and the term “ghost cells” had its origin in two American seminal articles by Thoma and Goldman in 1946. Although Gorlin et al. coined the term “calcifying odontogenic cyst” (COC) in 1962, this type of cyst was initially reported three decades earlier by Rywkind in Russia, and almost concurrently by Blood good in the United States and Sato in Japan. In 1948, Willis provided the initial histological evidence of a peripheral COC in his British pathology textbook. Credit for the earliest clinical presentation of odontoma associated calcifying cystic odontogenic tumor belongs to the American radiology textbook by Thoma in 1917.

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A Scandinavian journal report published in 1953 by Husted and Pindborg was the first to address a dentinogenic ghost cell tumor, and its peripheral counterpart was originally reported in the Swiss literature 7 years later. The current concept of COC was undoubtedly established by Gorlin et al. but the history of OGCL really started with Thoma’s pioneering work about a century ago.

Keywords Calcifying cystic odontogenic tumor · Calcifying odontogenic cyst · Dentinogenic ghost cell tumor · Early history · Odontogenic ghost cell lesions

Background

Most oral pathologists acknowledge that the first detailed account of calcifying odontogenic cyst (COC) was published in 1962 by Gorlin et al. [1], and Gold [2] also reported on COC in 1963. The former study stressed the histological resemblance of COC to cutaneous calcifying epithelioma of Malherbe [1], and the latter focused on the relationship between COC and calcifying epithelial odontogenic tumor [2]. Perhaps, the “keratinizing and COC” proposed by Gold [2] would be a fitting term for this interesting lesion. In consideration of Gold’s suggestion [2], Gorlin [3] in 1968 also used a similar compound name “calcifying and keratinizing odontogenic cyst” only once. Subsequently, many other designations have been suggested by different authors because of the diversity of clinicopathologic features [4–6], and the World Health Organization (WHO) classification of odontogenic tumors introduced the name “calcifying cystic odontogenic tumor (CCOT)” in 2005, a term which is in current use [7].

After the original reports of Gorlin et al. [1] and Gold [2], rapid progress was made, and a consensus began to

form that COC are comprised of two distinct entities; i.e., cystic and neoplastic lesions, and include a number of variants [4–6]. In view of these advances, the unified term “odontogenic ghost cell lesions (OGCL)” [5] or “ghost cell odontogenic tumors” [6], which refers to the origin and nature of these lesions and also defines their most characteristic microscopic feature, was proposed under the 2005 WHO guidelines [7]. The current view of OGCL suggests that four basic subtypes exist: (1) simple cysts (COC), (2) benign cystic tumors (CCOT), (3) benign solid tumors [dentinogenic ghost cell tumor (DGCT)]; and (4) malignant tumors (ghost cell odontogenic carcinoma) [4, 5]. This classification is not a consensus opinion and a topic of an international discussion [4–6, 8], but the overall term “OGCL” that covers all cystic and neoplastic variants and their combined lesions seems to be appropriate [4, 5]. A more recent reference supports this statement [9].

During a search for earlier literature about adenomatoid odontogenic tumor [10], we found many reports of OGCL that had not been included or discussed in any previous review articles [4–6, 11]. The aims of this study were to review and assimilate the published data, and to expand and revise the early history of OGCL.

Literature Review

The medical and dental literature published in the United States, Europe, and Japan was surveyed for early cases of OGCL using Google Scholar, Pub Med, and Index Cat. Since the so-called “COC” was generally diagnosed as a variant of ameloblastoma or a type of odontoma in the past [1–6, 11], the keywords odontogenic cyst, ameloblastoma, odontoma, and related diagnostic terms were employed during the search. We also examined the reference lists of journal articles and classic textbooks to retrieve additional cases [4–24, supplementary references 1–40]. The American literature did not contain much in the way of reports about odontogenic tumors and cysts until well into the 19th century; however, there were earlier reports from Europe [10, 19]. At that time, the term “odontoma” was used very loosely for all odontogenic cysts and tumors [12, 13, 15, 19].

As alluded to earlier, the distinction between OGCL and other odontogenic lesions that demonstrate ghost cell changes has been in a state of flux [4–6, 8, 25–34]. Different classifications of OGCL have been suggested, but some of them are complex and controversial [4–6, 8, 9]. Two international guidelines proposed by the WHO [7] and the Armed Forces Institute of Pathology [35] imply that all of the so-called “COC” are neoplastic in nature, and use “CCOT” [7] or “CCOT (DGCT) hybrids” [35] as a common term to include all combined lesions. However, the original name “COC” is suitable to describe simple

unicystic (non-neoplastic) OGCL that comprise about 80 % of reported cases [6], and the combined “CCOT” may behave differently depending on the type of the associated odontogenic tumors [4–6, 8, 9]. Accordingly, we decided to employ Praetorius’ classification scheme [5], which contains a more elaborated subclassification system [4, 6]. In the present study, the criterion for confirmed cases of OGCL was the conspicuous presence of ghost cells within the proliferating odontogenic epithelium based on a histologic description or photomicrographic presentation. Fully mature (completely formed) odontomas containing scattered ghost cells were excluded from our analysis.

Published Reports of OGCL Predating Gorlin et al. [1]

During the 45-year period from 1917 to 1962, 32 cases of OGCL were published (Table 1) [36–71], only six of which were included in the original review by Gorlin et al. [11]. Several authors interpreted Maitland’s case [72] to be an earlier example of OGCL [1, 11, 27], but we made exception of the acceptance because of no diagnostic accuracy. It remains unclear why Gorlin et al. [1, 11] felt compelled to exclude 4 out of the 5 cases of OGCL collected by Thoma and Goldman [40, 41] from their literature survey. A brief overview of the early history of OGCL was presented chronologically.

In 1917, Thoma [36] in Boston provided the first radiological evidence of CCOT associated with odontoma and added a radiograph of a similar CCOT in 1922 [37]. Both cases were documented multiple times in his subsequent textbooks [38, 39, 42–44] and review papers [40, 41]. Thoma [38] classified these lesions as follicular (dentigerous) cysts in 1934, but reclassified them as odontomas 7 years later [39]. In the European literature, Rywkind and Shiltzow [46] in Moscow provided an excellent account of CCOT associated with odontoma, which included superb photomicrographs, in 1931. In the same year, Chompret and Dechaume [45] in Paris reported that their odontoma associated CCOT shared morphological features with calcifying epithelioma of Malherbe. The following year, Rywkind [47] produced the first report detailing the histology of COC, which he considered to be the same kind of lesion as cholesteatoma of the ear. This name was used again in 1934 by Aronson in Moscow [51].

The cases reported by Blood good [48] and Sato [49] in 1933 were the initial reports of COC from the United States and Japan, respectively. The former surgeon in Baltimore made the first mention of recurrence [48]. Fifteen years later, the earliest textbook description of the gingival occurrence of COC was produced by Willis [59] in London, and he believed it to be an early squamous-cell growth of gingival epithelial residues. In 1953, Husted and Pindborg [62] in Copenhagen provided the original report about a case of

Table 1 Reports of OGCL predating Gorlin et al. [1] worldwide

Year	Cases in literature	Original diagnosis ^c	Current diagnosis ^d
1917	Thoma [36], Fig. 190	Dentigerous cyst	CCOT + odontoma ^a
1922	Thoma [37], Fig. 322	Cystic odontomata	CCOT + odontoma ^a
1931	Chompret and Dechaume [45], case I	Odontome adamantin	CCOT + odontoma
1931	Rywkind and Shiltzow [46]	Odontome	CCOT + odontoma
1932	Rywkind [47] ^e	Cholesteatome	COC
1933	Bloodgood [48], Fig. 19	Solid/cystic adamantine epithelioma	COC
1933	Sato [49]	Folikullarcyste	COC
1933	Masaki [50], Figs. 6–8	Adamantinom	DGCT ^b
1934	Aronson [51]	Cholesteatome	COC
1934	Fujibayashi and Ninomiya [52]	Follikulären Zahncysten	CCOT + odontoma
1938	Ch'in [53], Fig. 9	Squamous-celled adamantinoma	COC ^b
1942	Hirayama [54]	Odontoma with follicular cyst	CCOT + odontoma
1944	Enomoto et al. [55]	Cyst with odontoma and ameloblastoma	CCOT + odontoma
1944	Yamamoto and Hama [56]	Zahnlosen Follikulärezyste	CCOT + odontoma
1946	Thoma and Goldman [40, 41], cases 50 and 52 ^e	Odontogenic mixed tumor	CCOT + odontoma
1948	Bernier and Ash [57], Fig. 154A	Calcification of degenerated ameloblastoma	COC
1948	Stones [58], Fig. 766	Adamantinoma showing epithelial pearls	COC
1948	Willis [59], case VII	Intra-alveolar epidermoid carcinoma	Peripheral COC
1951	Handousa [60], case XIII	Squamous cell adamantinoma	COC
1951	Okamoto [61]	Follicular cyst and odontoma	CCOT + odontoma
1953	Husted and Pindborg [62], case 11 ^e	Mixed odontogenic tumour	DGCT
1953	Frissell and Shafer [63]	Ameloblastic odontoma	CCOT + ameloblastic fibro-odontoma
1956	Pflüger [64], case 5	Odontom	CCOT + ameloblastic fibro-odontoma
1957	Dechaume et al. [65], case 16	Adamantinome solide dentifié	CCOT + odontoma
1957	Ishikawa [66], Fig. 14	Ameloblastoma	DGCT ^b
1958	Kasai and Nomura [67]	Follicular cyst	COC
1959	Boss [68] ^e	Ameloblastoma	COC
1960	Spirgi [69] ^e	Épithélioma adamantin calcifié	Peripheral DGCT
1960	Thoma and Goldman [44], Fig. 1295	Cystic ameloblastoma with calcifications	COC
1961	Lurie [70] ^e	Melanotic progonoma	CCOT + odontoma
1962	Jurgens [71]	Odontoma	CCOT + odontoma

^a Photomicrograph was presented in 1934 [38]

^b These 3 cases were difficult to subdivide because of limited data

^c Most terms were dated, but listed without modification

^d Diagnostic terms are taken from Prætorius' classification [4, 5]

^e These 6 cases were included in the literature review by Gorlin et al. [11]

OGCL odontogenic ghost cell lesions, CCOT calcifying cystic odontogenic tumor, COC calcifying odontogenic cyst, DGCT dentinogenic ghost cell tumor

DGCT involving recurrence, but no studies about its peripheral counterpart were published until 1960 [69]. Between 1917 and 1962, acceptable cases of ghost cell odontogenic carcinoma were not reported in the literature.

The Concept of Ghost Cells

There is no doubt that the term “ghost cells” in OGCL was introduced by Thoma and Goldman [40, 41] in 1946. As the

number of cases increased, Gorlin et al. [1] began to call COC as “oral Malherbe” by the 1950s, and many authors have drawn attention to the unusual “ghosting” of the odontogenic epithelium seen in such lesions [4–6]. A nucleated ghost cells have been referred to in the English literature using a variety of terms, including “degenerated epithelium” [44, 57], “epithelial pearls” [53, 58], “enamel organ” [60], “concentric homogenous bodies” [62], “calcified globules resembling keratin” [63], “hyaline-like bodies” [71], and “keratinized squamæ” [2], to name a few.

In the German literature, Rywkind and Shiltzow [46] introduced the name “rote Zellen” (red cells) for ghost cells in 1931. This nomenclature was originally applied to the undifferentiated epithelial cords of adamantinomatous craniopharyngiomas [64]. Soon after, the term “verhornte Epithelzellen” (keratinized epithelial cells), which more accurately reflected the origin and nature of ghost cells, was proposed by Rywkind [47]. He also recognized that these cells can provoke foreign body giant cell reactions. In the United States, the concept of a “ghost epithelium” was introduced in a histological study of ameloblastoma by Robinson [73] in 1937. Furthermore, he adopted the term “ghost cells” to describe the degenerative changes that take place in the stellate reticulum during the early stages of microcyst formation. However, Robinson’s suggestion did not gain much traction or attention. Although Thoma [40, 41] in 1946 came to the conclusion that ghost cell keratinization is caused by necrobiosis of the odontogenic epithelium preceding calcification, it is curious that no mention of ghost cells appeared in the 3rd (1950) [42], 4th (1954) [43], or 5th (1960) [44] editions of his textbooks.

Conclusion

In light of the information we collected during this review, we emphasize Thoma’s [36–44] significant contribution to modern knowledge about OGCL. We also consider that CCOT associated with odontoma might not be as rare as other “combined” lesions. It is worth noting that until the early part of the 20th century, the soft tissue components of lesions were not examined histologically, and ghost cell epithelia (if they were present) were overlooked since odontomas were not sectioned in most cases [43, 44]. Supplementary Table 1 summarizes 40 reports of cysts and cystic tumors with otherwise typical clinical presentations of OGCL (diffuse calcification or small odontoma formation) that were published in the American and European textbooks and journals from 1838 to 1958 [65, supplementary references 1–40]. Although there is currently no way to confirm them, several of the lesions are likely to have involved OGCL. It is hoped that additional early references found during this study will be incorporated into OGCL databases.

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