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Research article

Hybrid odontogenic lesions: A case series of a rare entity

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ABSTRACT

Background: The occurrence of hybrid odontogenic lesions with two or more morphologically distinct components is a rare phenomenon and poses a diagnostic challenge. We aimed to study the clinical, radiological, and pathological features and behavior of hybrid odontogenic lesions, to enhance awareness about these rare lesions.
Method: Hematoxylin and Eosin slides of hybrid odontogenic lesions diagnosed between January 01, 2012 and December 31, 2020, were reviewed. Demographic and radiological information were obtained from the patient's medical records.
Results: 8 cases were diagnosed with a mean age of 19.1 years and male to female ratio of 1:1.7. Involvement of mandible was more common (n = 5) as compared to maxilla (n = 3). All patients presented with swelling for an average of 9.75 months (3–25 months) duration. Bleeding, loose teeth, pain and facial asymmetry were reported in 5,3, 3, and 2 cases, respectively. Radiologically, 7 cases were well demarcated, 75% cases (n = 6) were radiolucent, and average radiological size was 4.8 cm. All patients were managed with surgery alone. 5 cases (62.5%) underwent enucleation and curettage, while local excision, en-block resection and segmental mandibulectomy were performed in 1 case each. Histologically, ossifying fibroma/cemento-ossifyiong fibroma were the most lesion, occurring in 5 cases (62%), followed by giant cell granuloma like lesions (GCG) i.e., central and peripheral giant cell granuloma (n = 3), Adenomatoid Odontogenic tumor (AOT) (n = 2), and DC (n = 2), ameloblastic fibroma (AF) (n = 1), Ameloblastoma (n = 1), calcifying odontogenic cyst (COC) (n = 1), and complex odontoma (n = 1). No evidence of recurrence was noted after 4–99 months of surgery (mean: 32.9) in cases with available data (n = 7). Long-term complaints included facial asymmetry (n = 2) and pain (n = 1).
Conclusion: Most hybrid odontogenic lesions affect young females in the second decade of life and commonly show COF and OF as hybrid components. A conservative approach to management appears adequate.

1. Background

Odontogenic lesions are relatively uncommon and account for approximately 4% of all head and neck biopsies. Among these, cysts are far more prevalent than tumors, comprising 84% and 16 % of cases, respectively. Nearly two-thirds of these lesions are diagnosed as radicular cyst, followed by dentigerous cyst (DC), odontogenic keratocyst, ameloblastoma and odontoma. Other entities are

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extremely rare and collectively account for about 3.7% of all odontogenic tumors [1].

Odontogenic tissue develops through time-dependent, closely regulated interactions between epithelial and mesenchymal elements and therefore, lesions arising from this tissue show a wide variety of morphologies [2–4]. Notably hybrid lesions, comprising of two or more distinct areas exhibiting characteristic morphologic features of different entities, are rare and when present, pose a diagnostic challenge. Although many hybrid lesions have been reported, their frequencies and combinations are not well documented [5,6]. This series reports 8 cases of hybrid odontogenic lesions from a tertiary care center in a developing country.

2. Material and method

Cases labelled as mandible, maxilla, face, or jaw and diagnosed as any odontogenic cyst and tumors, between January 01, 2012 and December 31, 2020, were retrieved from electronic hospital information system of the Pathology Department of the Agha Khan University Hospital (AKUH). Among these, cases with any combination of two different diagnoses were selected. Permission from the hospital ethical committee was obtained. Slides and paraffin blocks were pulled out from departmental archives and reviewed. Diagnoses were independently verified by the senior authors. Clinical data such as age, gender, signs, and symptoms were collected from the clinical history section of pathology reports. Radiological images, details of treatment and follow-up data were obtained from medical records.

3. Results

A total of 8 cases were diagnosed in the study period. Mean age was 19.1 years (range: 8–42 years, male: 22.7 years, Female: 17.0 years). Male to female ratio was 1:1.7. Involvement of mandible was more common (n = 5) as compared to maxilla (n = 3). All patients presented with slowly growing swellings with an average evolution time of 9.75 months (3–25 months). Bleeding, loose teeth, pain and facial asymmetry were reported in 5,3, 3, and 2 cases, respectively. Radiologically, 7 cases were well demarcated, and one case showed ill-defined margins. 75% cases (n = 6) were radiolucent, whereas the remaining 2 cases showed mixed radiolucent and radiodense appearance (Figs. 1A, 2A and 3A,4A,5A,6A). Radiological size of these lesions ranged from 2.8 cm to 7.5 cm (mean: 4.8 cm). All patients were managed with surgery alone. 5 cases (62.5%) underwent enucleation and curettage, while local excision, en-block resection and segmental mandibulectomy were performed in 1 case each. Histologically, ossifying fibroma/cemento-ossifyiong fibroma were the most common lesion, occurring in 5 cases (62%) (Figs. 1–3), followed by giant cell granuloma like lesions (GCG) i.e., central and peripheral giant cell granuloma (37%) (Figs. 1 and 4), adenomatoid odontogenic tumor (AOT) (25%) (Fig. 2), and DC (25%) (Figs. 3 and 5). 1 case each of ameloblastoma (Fig. 4), complex odontoma (Fig. 5) ameloblastic fibroma (AF) (Fig. 6), and

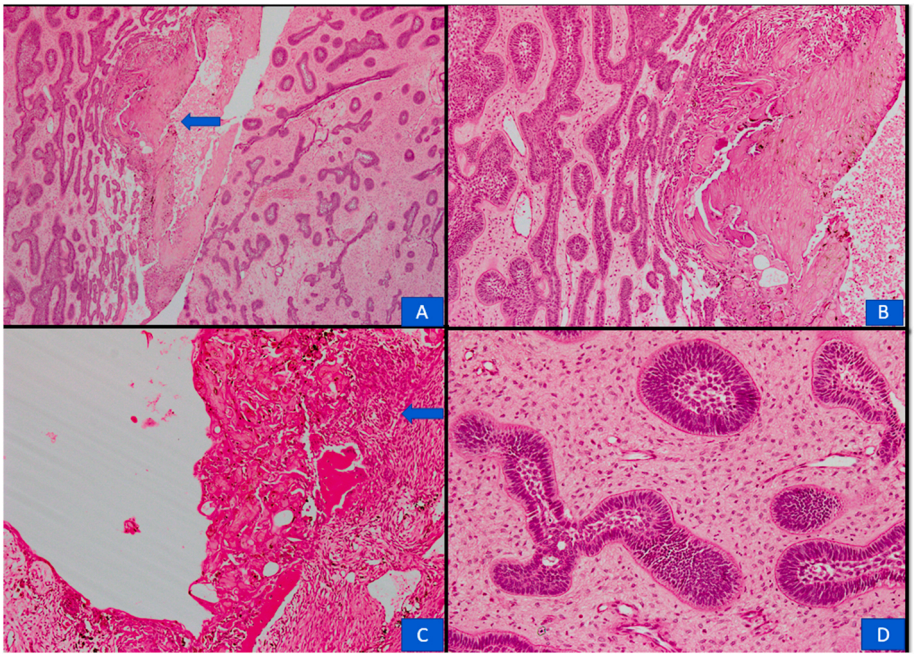

Fig. 1. A) OPG shows a well-circumscribed lesion with and impacted tooth in the body of mandible. The margins are sclerotic. Lesion has a mixed radiodensity. Low power (B, H&E) and high power (C, H&E) image shows a sharply demarcated hybrid lesion composed of a fibro-osseous lesion (←) and giant cell rich lesion (→). Surface mucosa can be seen in the left bottom of (↑). High power images showing PGCG with osteoclast-like giant cells surrounded by mononucleated cells and extravasated red blood cells (D, H&E). (E, H&E) shows high magnification of COF, exhibiting deposits of cementum and osteoid with intervening fibrous tissue.

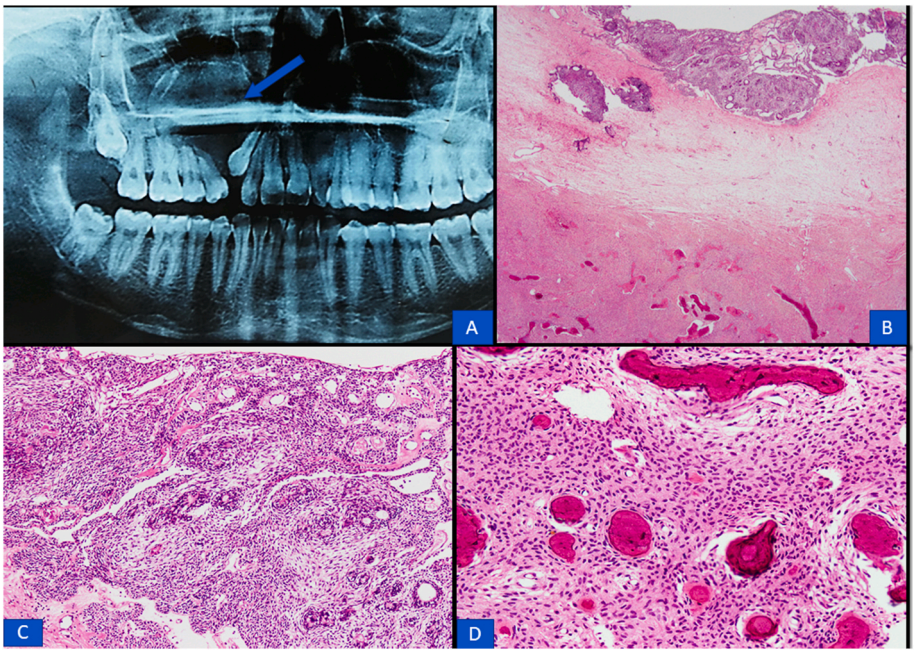

Fig. 2. A) OPG showing a sharply delineated radiolucency, associated with the root of unerupted canine. B) Low power image of the tumor exhibiting nodular aggregates of epithelial cells (top) and fibro-osseous lesion (bottom) (H&E). The nodules are composed of tubular structures and sheets of oval to spindle cells representing AOT (C, H&E)) and the fibro-osseous lesion is COF which is composed of spherules and trabeculae of densely mineralized material surrounded by bland looking fibroblastic population (D, H&E).

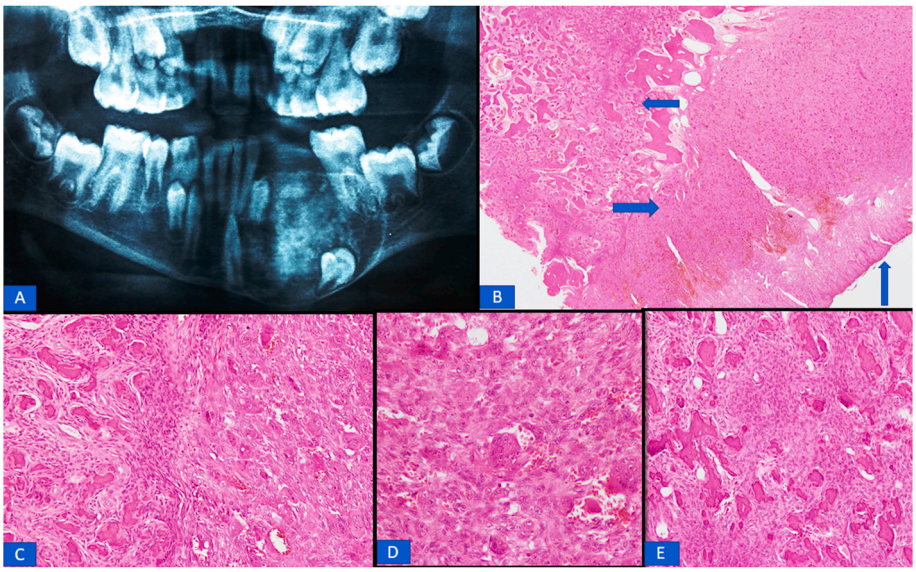

Fig. 3. (A) OPG shows a large well-circumscribed predominantly cystic lesion extending. from left canine to right first molar. An ill-defined lighter area with a hint of minute. radiodensities is seen at the base of the lesion. An impacted tooth is also noted (←). (B, H&E) Cystic area shows stratified squamous lined cyst with elongated rete ridges representing DC, whereas adjacent areas show irregularly shaped trabeculae of woven bone surrounded by sheets of relatively monotonous spindle cells arranged in short bundles and fascicles representing ossifying fibroma (C&D, H&E).

calcifying odontogenic cyst (COC) (Fig. 6) were also noted. Follow-up information was available for 7 cases. No evidence of clinical or radiological recurrence was noted after 4–99 months of surgery (mean: 32.9). Long-term complaints included facial asymmetry (n = 2) and pain (n = 1). Details demographics, presenting symptoms, radiological features, pathological diagnosis and follow-up data are given in Table 1.

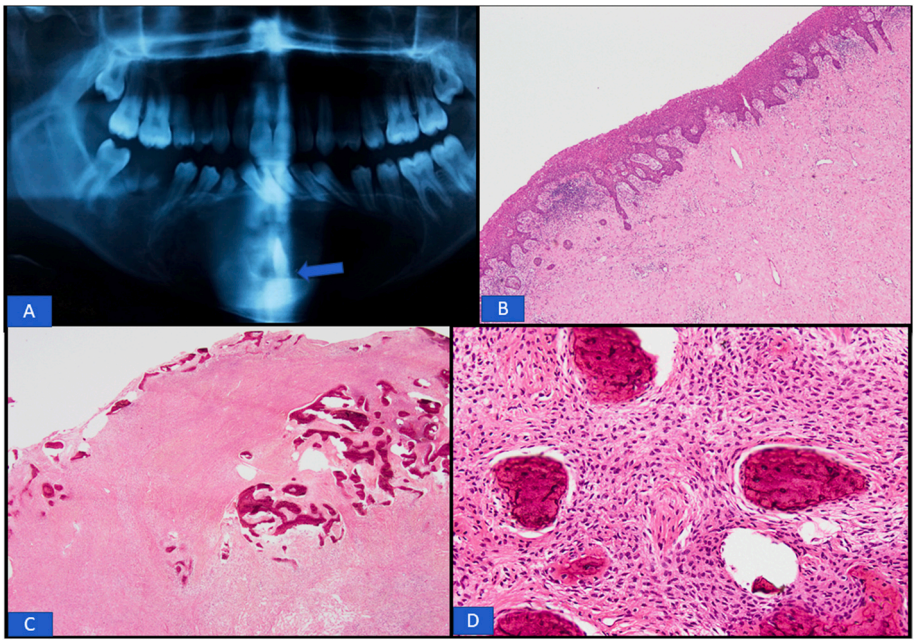

Fig. 4. (A) CT scan (Sagittal plane) showing an expansile lesion involving the maxilla with nasal extension, effacement of the maxillary sinus and alveolar process. No calcifications are noted. (B, H&E) Anastomosing trabeculae of epithelial cells with basal regimentation and central stellate reticulum, focally showing squamous differentiation (not shown in image). (C, D, H&E) Low and high-power images showing a discrete mass with giant cell rich morphology (←) with overlying ameloblastic epithelium (↑). Many osteoclast-like giant cells are seen surrounded by spindle to histiocytoid mononucleated cells, fibroblasts and inflammatory cells.

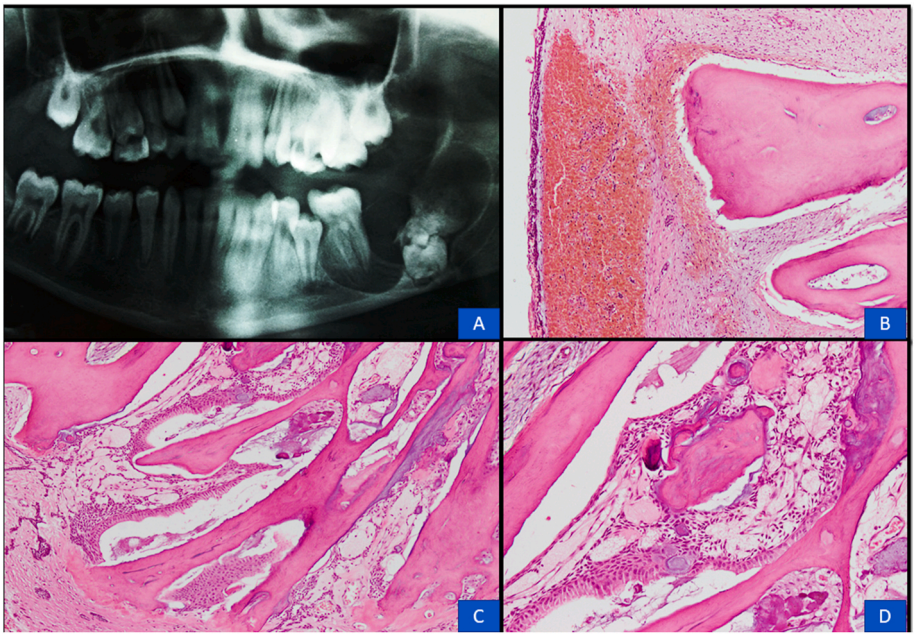

Fig. 5. (A) OPG showing well delineated, mixed radiopaque and radiolucent, partly cystic. lesion involving angle of mandible. (B, H&E) Low power image of the lesion shows mineralized dental material (left) with a cystic lesion lined by odontogenic epithelium. (C, H&E) and (D,H&E) show high magnification images of complex odontoma with dentin, enamel epithelium and intervening stroma.

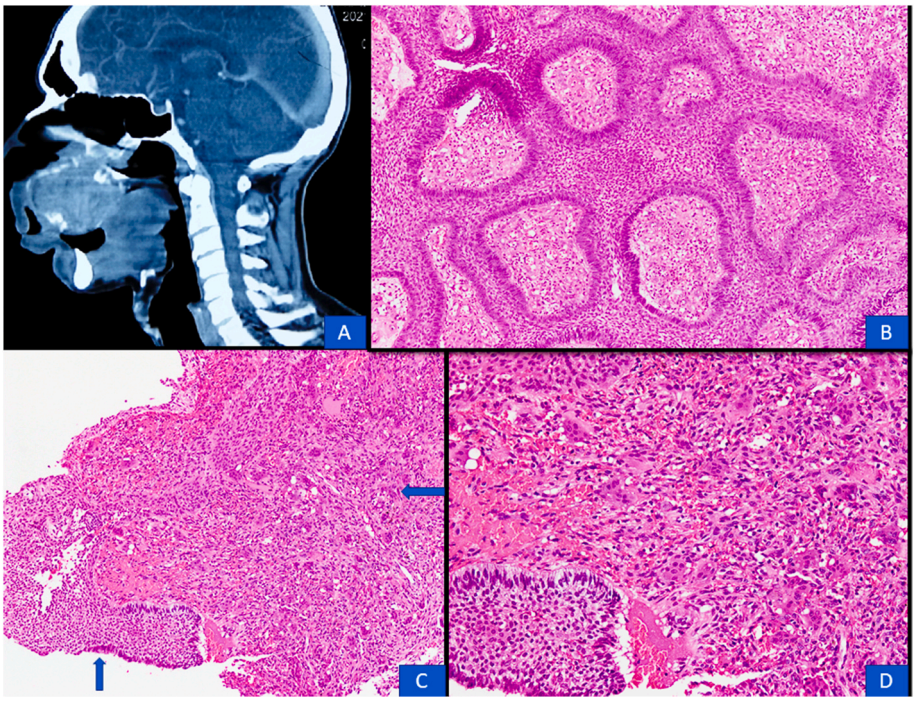

Fig. 6. Hematoxylin and eosin (H&E) stained section A) Low power and B) intermediate. power views showing surface squamous epithelium of COC (←) with underlying biphasic.lesion. C) high power of cyst wall covered by ghost cells and basal ameloblastic epithelium (←). D) high power image of underlying biphasic lesion shows nests and strands of ameloblastic.epithelium with peripheral palisading and central stellate reticulum embedded in a myxoid. stroma with spindle to stellate cells.

Table 1
Summary of Hybrid odontogenic lesions (n = 08).

No	Age (yrs)	Sex	Site	Size	Symptoms	Radiology	Diagnosis	Surgery	Follow-up
1	8	M	Mandible	4.4	Left sided face swelling, 5 months. Dull pain, mobile teeth	Radiolucent cyst Well-defined	AF + COC	Enucleation curettage	RF at 99 months
2	19	F	Maxilla	2.8	Swelling upper jaw, 4 months, painless	Radiolucent Well-defined	AOT + OF	Local excision	RF at 8 months
3	18	M	Maxilla	5.5	Swelling upper jaw, 11 months, painless, bleeding	Radiolucent Well-defined	AOT + COF	Enucleation curettage	RF at 64 months
4	9	F	Mandible	7.5	Left sided face swelling, 8 months. Painful, bleeding, facial asymmetry, loose teeth	Radiolucent with focal opacity Well-defined	PGCG + COF	Enucleation	NA
5	25	F	Mandible	4.8	Left lower jaw swelling, 25 months, bleeding, painless	Ill-defined Mixed density	CGCG + COF	Segmental mandib	RF at 21 months
6	18	F	Mandible	5.2	Hard painless swelling, facial asymmetry, bleeding, 17 months,	Radiolucent Well-defined	DC + OF	Enucleation	RF at 9 months
7	14	F	Mandible	3	Hard, painless, 3	Mixed Well-defined	DC + Complex odontoma	Enucleation	RF at 25 months
8	42	M	Maxilla	5.6	Swelling, painful, loose teeth, bleeding, 5 months	Radiolucent Well-defined	Ameloblastoma + CGCG	En block resection	RF at 4 months

RF: Recurrence free.

4. Discussion

Hybrid odontogenic lesions are rare. In a recent systematic review, Pontes et al. found only 203 cases in the literature, with mean age was 24.5 years and male to female ratio was 1:1:5 [7]. Comparatively, our patients were younger with a similar gender distribution. In this review, swelling (80%) and pain (12%) were the leading symptoms and tooth mobility (1%) was rare. All our cases presented with swelling which was painful in 3 cases. However, tooth mobility was more frequent in our patients (37%). As compared to the above-mentioned study, our patients had a longer evolution time (9.75 months vs 8.2 months) and had the same average tumor size (4.8 cm). Nearly three-fourths of all cases included in this study were radiolucent, similar to our finding of 75%. Involvement of

maxilla and mandible was reported to be 42% and 58%, respectively, in accordance with our findings (38% and 62%).

Histopathologically, the most reported hybrid odontogenic lesion is COC, an otherwise very rare cyst accounting for less than 1% of all odontogenic lesions, frequently combined with odontoma [7–13]. This association was seen in 24% of COCs in a study by Hirshberg et al. Due to the high relative frequency of this association, distinct radiological appearance, earlier age of presentation and unique morphology of hybrid lesions, they suggested reclassifying these as a separate entity named 'odontocalcifying odontogenic cyst' [14]. Hybrid Ameloblastoma and COC is the next most common combination after odontoma [15,16]. In our series, only one case showed a COC component, which was associated with AF. This patient was an 8 years-old boy with slowly growing, mildly painful, radiolucent swelling of mandible with mobile overlying teeth. He underwent curettage and is recurrence free 99 months after surgery. Previously, 8 cases of hybrid COC and AF have been reported in the literature. Including our patient, 5 were male and age at presentation ranged between 3 and 10 years. All patients presented with swelling with two reporting tooth mobility and 01 with dull pain and equal involvement of mandible and maxilla. Radiologically, the majority are radiolucent. following surgery, no recurrence was seen after follow-up period ranging from 1 year to 8 years [7,17–21]. Overall, hybrid COC and AF affects young patients and no documented evidence of recurrence after conservative surgery. Nevertheless, COC can potentially transform into ghost cell odontogenic carcinoma. Thus, correct diagnosis and complete enucleation are very important [22–24].

COF/OF were in fact the most frequently encountered lesions in our study and were seen in 5 cases, combined with AOT (n = 2), GCG (n = 2), and DC (n = 1). AOT is a rare odontogenic tumor affecting young, predominantly female patients and commonly involving anterior maxilla. It is often clinically diagnosed as a cyst and there is a well-documented association with an unerupted tooth [25]. AOT can present as hybrid with many other tumors, including COC, ameloblastoma and odontoma [5,7,26–34]. Hybrid AOT and OF/COF are, however, controversial. Li et al. reported the first case of AOT with concomitant fibro-osseous lesion in a 22-year-old girl. This was a 4.5 cm, radiolucent maxillary tumor with cystic central areas and solid periphery. Morphological features classical of AOT were noted in the center and that of were identified at the periphery, surrounding the central areas of AOT in an eggshell-like manner. Patient had no recurrence after 5 years of follow-up. Due to clear demarcation of two distinct areas along with similar behavior as usual AOTs, they deduced that fibro-osseous proliferation in association with AOT should be regarded as a mesenchymal induction of adjacent tissue by the later and not as a true hybrid lesion [35]. 2 similar cases were described by Naidu et al. as well [36]. In contrast, both of our cases had expanded areas of fibro-osseous lesion that appear intermingled with those of AOT and no eggshell-like peripheral, circumferential distribution was noted. The fibro-osseous lesions were also distinct from the stromal elements of AOT.

Additionally, the majority of large AOTs are not associated with induction of fibro-osseous changes. Furthermore, recurrence is considered rare in OF and COF as well and therefore, does not rule out the diagnosis of hybrid tumor [37,38]. Our cases presented as a single radiolucent lesion, clinically. Therefore, it is our understanding that these are best classified as hybrid tumors representing two distinct neoplastic processes.

Hybrid OF/COF and GCG is better recognized, and we found 5 reports in literature, describing 7 such cases [39–43]. The pathogenesis of these tumors is not well understood. Based on mandibular molar/pre-molar location and presence of spindle cells in transitional areas, Kaplan et al. hypothesized that COF is the primary lesion in hybrid COF-GCG tumors [41]. Further studies highlighted the role of cytokines released by osteoblasts and stromal spindle cells in giant cell differentiation and activation, thus supporting the above hypothesis [40,44,45]. These hybrid tumors present at a mean age of 38.5 years (range 5–68 years) with a slight female predominance. 71% tumors arise in mandible and over half involve pre-molar area. surgical resection was done in majority of cases (6 out of 7) and recurrence was infrequent as only 1 case recurred within 1 year of resection [39]. Clinical data in our case is in accordance with these findings. Both patients were females with a mean age of 17 years and mandibular tumors. One patient had hybrid COF and PGCG and was lost to follow-up, whereas the other patient was diagnosed with COF and CGCG. She underwent segmental mandibulectomy and is recurrence free 21 months after surgery.

DC is the second most common odontogenic cyst after radicular cyst [1]. These cysts can rarely harbor foci of ameloblastoma in the epithelial lining [46]. Our case shows a sclerotic osseous rim around the cyst on radiology and distinct areas of in close relation with cyst wall on histopathology. Possible mechanisms for this occurrence include reactive fibro-osseous changes due to sustained insult of enlarging cyst to the surrounding mesenchymal tissue and collision to two distinct pathologies at the same site. However, the presence of fibro-osseous proliferation around a DC is not reported in the literature. In a study of 2082 cases of DC by Zhang et al. no cases were associated with such stromal reaction, speaking against the first hypothesis [47]. Other studies on various odontogenic cysts and tumors also lack any description of such reactive processes. In our experience, this is the first case to show such striking and unequivocal morphology. Therefore, we consider these as independent processes presenting as hybrid lesion.

Hybrid DC and odontoma are relatively better known. We observed this hybrid lesion in a 14-years old girl with clinical, radiological and histological features very similar to the case reported by Ricardo et al. who in their publication, concluded that these were indeed true hybrid lesions [48]. Few other authors have also reported cases of odontomas with DC-like cystic areas and labelled them as DC arising in odontoma or vice versa. However, these lesions may also fall under the category of hybrid lesions rather than actual transformation of odontoma into a cyst with epithelial lining resembling DC [49–51]. In the study by Pontes et al. 12 such cases were acknowledged as true hybrid lesion. These cases had a mean age of 26 years (range: 5–58 years) and no recurrence was documented [7]. Similarly, our patient has no sign of recurrence 25 months after enucleation. Both DC and odontoma are benign lesions and lack significant risk of recurrence, therefore, conservative management appears to be adequate, Diagnosis of a true hybrid ameloblastoma and GCG requires the presence of a distinctly neoplastic giant cell-rich lesion admixed with epithelial tumor, while presence of scattered giant cells at the periphery of a solid ameloblastoma is considered to be a reactive process. These reactive giant cells show evidence of histiocytic origin and do not form a distinct mass lesion [52]. Nevertheless, GCG has been reported as a component of hybrid lesions with other odontogenic tumors such as odontogenic fibroma and odontogenic keratocyst [53,54]. Stuepp et al. recently reported a hybrid ameloblastoma and CGCG in a 67-years woman who presented with a hard swelling of mandible [55]. Similar to our

case, this was painless and on OPG showed a well-delineated lytic mass. Enucleation was performed and information regarding follow-up is not published.

As ameloblastoma can be locally aggressive, we believe that the optimal management of hybrid lesions including an ameloblastoma component should follow the guidelines for conventional ameloblastoma. Although clinical and radiological data was meticulously collected, detailed surgical notes were missing from some files. The limitations of this study include lack of access to complete pre- and post-operative imaging studies, surgical notes and follow-up data in a few cases. Immunohistochemical staining and molecular studies were also not done to further assess the pathogenesis of these lesions.

5. Conclusion

- Most hybrid odontogenic lesions affect young females in the second decade of life.
- Mandible is more commonly involved as compared to maxilla.
- The most common hybrid components are Cemento-ossifying Fibroma and Ossifying Fibroma.
- A conservative approach to management appears adequate.

Ethics approval and consent to participate

All procedures performed on patient tumor samples in this study were in accordance with the ethical standards of the Institute Ethics Committee (ERC) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The study was approved by ERC of AKU (2021-6030-17148). Informed consent was obtained in patients in whom follow up was available.

Consent for publication

Written informed consent was obtained.

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Author contribution statement

Muhammad Raza: Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Arsalan Ahmed: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Jamshid Abdul-Ghafar: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data, Did the final review and took the responsiblity of corresponding author.

Rashida Ahmed: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Nasir UdDin: Conceived and designed the experiments; Performed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Abbreviations

H&E; Hematoxylin and Eosin, COF; Cemento-ossifying fibroma, AOT; Adenomatoid odontogenic tumor, CGCG; Central giant cell granuloma, PGCG; Peripheral giant cell granuloma, OF; Ossifying fibroma, DC; Dentigerous cyst, OPG; Orthopantomogram, AF; Ameloblastic fibroma, COC; Calcifying odontogenic cyst; CT; Computed tomography; AKUH; Aga Khan University Hospital.

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