The Clinical and Radiological Spectrum of Glandular Odontogenic Cysts: A Multicenter Study of 92 Cases

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ABSTRACT

Objective: The purpose of this multicenter retrospective study was to report the clinical and radiological features of 92 glandular odontogenic cysts (GOCs) diagnosed over a 20-year period.

Study Design: Histologically confirmed cases of GOC were retrospectively reviewed from four Oral Pathology laboratories in South Africa and Brazil to categorize the clinical and radiological spectrum of GOCs.

Results: The mean age of patients was 46 years (range 17-87) with a male-to-female ratio of 1.2:1. GOCs had a mandibular predilection (68%), with 42% of all cases located anteriorly. Additionally, 42% of cases crossed the midline. Radiologically, most lesions were unilocular (53%) and uniformly radiolucent (97%), with well-demarcated borders (93%). Loss of cortical integrity (71%), as well as maxillary sinus (67%) and nasal cavity encroachment (72%), were common findings. Significant differences in lesions between the two countries were discovered in sex predilection, clinical signs and symptoms, and lesion locations within the mandible and maxilla.

Conclusion: GOCs present with a wide spectrum of clinical and radiological features, ranging from lesions with typical GOC-like presentations to more aggressive lesions. The need for advanced imaging in the surgical planning of GOCs exhibiting radiological signs of aggression is justified based on the high recurrence rate.

Keywords: Odontogenic cysts, Glandular odontogenic cyst, Maxillofacial Radiology, Oral and Maxillofacial Pathology

INTRODUCTION

The glandular odontogenic cystS (GOCS) are developmental lesions arising from remnants of the dental lamina that contain features of glandular differentiation in their lining. The entity was first reported by Padayachee *et al* in 1987 as 'sialo-odontogenic cyst' and was later designated GOC by Gardner *et al* in 1988.[1,2] GOCs frequently affect patients during the 5th to 7th decades of life with a slight male predilection.[3,4] They present as asymptomatic swellings often located in the anterior mandible with a tendency to cross the midline.[3,5] When the maxilla is affected, GOCs tend to occur in a globulomaxillary relationship.[6,7] Radiologically, they present as well-demarcated unilocular, or less often multilocular, radiolucent lesions.[3,6,7] Bony expansion is common, whereas tooth displacement, root resorption, and cortical perforation are infrequent findings.[3,7]

GOCs may pose diagnostic difficulties as they share overlapping histological features with other intraosseous entities. These include the lateral periodontal cyst and its botryoid variant, and the dentigerous cyst with metaplastic changes.[4] Fowler *et al* proposed a set of ten histological criteria to distinguish GOCs from other GOC-mimickers.[4] Importantly, GOCs also share overlapping histological features with central mucoepidermoid carcinoma (MEC), a rare malignant intraosseous neoplasm. Some authors speculate that GOC and central MEC represent a biological spectrum of the same entity.[4,5] This is supported by the aggressive radiological presentation and high recurrence rate often seen in GOCs.[4,8,9] This issue raises a diagnostic dilemma, as the distinction between these lesions is critical for treatment approach and patient prognosis. Bishop *et al* partially resolved this controversy by establishing that GOCs lack the *MAML2* gene rearrangements that are often seen in MECs.[10] However, later investigations found that these rearrangements can be negative in approximately 32% of MECs.[5,11] Furthermore, *MAML2* rearrangements that were not present in primary GOCs were subsequently detected in recurrent GOCs or apparent MECs arising from GOCs.[12,13] Reddy *et al* argued that *MAML2* rearrangement inconsistencies have made molecular analysis unreliable in differentiating between these two entities.[5]

Ultimately, histological features must be correlated with the clinical and radiological information

to render an accurate diagnosis. Reddy *et al* emphasized that location and clinical signs are important distinguishing parameters between GOCs and central MECs.[5] In contrast to the typical presentation of GOCs, central MECs present as painful swellings in the mandibular posterior body-ramus complex, often in association with impacted teeth.[14] A systematic review of the literature revealed limited radiological information on the effects on surrounding structures in reported cases of GOCs.[15] This information is regarded as useful in assessing the biological behavior and potentially aggressive nature of GOCs.

GOCs are usually treated by conservative surgical enucleation, but this approach has resulted in a high propensity for recurrence.[3,4,9] Approximately 21-50% of GOCs recur, with a reported mean period of recurrence of 62 months.[3,4,9] Therefore, the recurrence rate of GOCs may be underreported, as the majority of cases in the literature only report a 24-month follow-up period.[16] Higher recurrence rates have been reported for multilocular lesions and lesions exhibiting bony expansion and cortical perforation.[3,9] Following a review of treatment and recurrences, Kaplan *et al* recommended that enucleation might be sufficient for small unilocular GOCs, whereas peripheral ostectomy/marginal resection is recommended for larger multilocular lesions.[9] This points to the need for advanced imaging modalities in extensive and multilocular lesions to assist in surgical planning. The high recurrence rate necessitates a 3-7 year follow-up period for confirmed GOC cases.[9]

Recently, there has been an increased interest in GOCs with atypical presentations to better understand their clinical spectrum. To date, approximately 169 well-documented cases of GOCs have been published, as reported in a recent review.[3] The purpose of this multicenter retrospective study was to report the demographic, clinical, and radiological features of 92 GOCs diagnosed over a 20-year period, representing the largest single study series to date. An epidemiological investigation of GOCs, with an emphasis on the clinical and radiological features, will be advantageous in the diagnostic process, surgical planning, and ultimately overall prognosis.[3]

MATERIALS AND METHODS

The study was conducted following approval by the University of Pretoria, Faculty of Health Sciences Research Ethics Committee (Reference number: 876/2020). All procedures followed the ethical standards of the Helsinki Declaration of 1975, as revised in 2008.

Histologically diagnosed cases of GOC acquired over a 20-year period (2000-2020) were retrospectively reviewed. Cases were collected from the archives of four Oral Pathology laboratories from two countries: South Africa (University of Pretoria) and Brazil (Federal University of Rio de Janeiro, Federal University of Minas Gerais, and University of Campinas). The histological diagnoses of the included cases were confirmed by experienced Oral and Maxillofacial Pathologists at each institution based on the criteria described by Fowler *et al*[4], as illustrated in Fig. 1. Cases with insufficient clinical data and/or inconclusive histological features to render a diagnosis of GOC were excluded from the study.

Of the 50 cases from South Africa, 7 did not meet the histological criteria to render a definitive diagnosis of GOC and were excluded from the study. Review of the 62 lesions diagnosed as GOC at the 3 Brazilian universities revealed that 13 cases did not meet the histological criteria and were also excluded. As a result, the study included 43 cases from the University of Pretoria and 49 from the Brazilian institutions (25 from the Federal University of Rio de Janeiro, 15 from the Federal University of Minas Gerais, and 9 from the University of Campinas), for a total of 92 cases.

The prevalence of GOC among diagnosed head and neck lesions was calculated at each institution. Demographic and clinical data, including mean age, sex, clinical signs and symptoms, mean duration, and lesion site were retrieved from the clinical records from each university. Radiographic examinations utilized in this study included intraoral and panoramic radiographs as well as cone beam computed tomography (CBCT). Radiological findings were assessed in a similar manner as in the systematic review by MacDonald-Jankowski[15] to ensure consistency with the current literature. The borders, locularity, radiodensity, and effects on surrounding structures were obtained from available

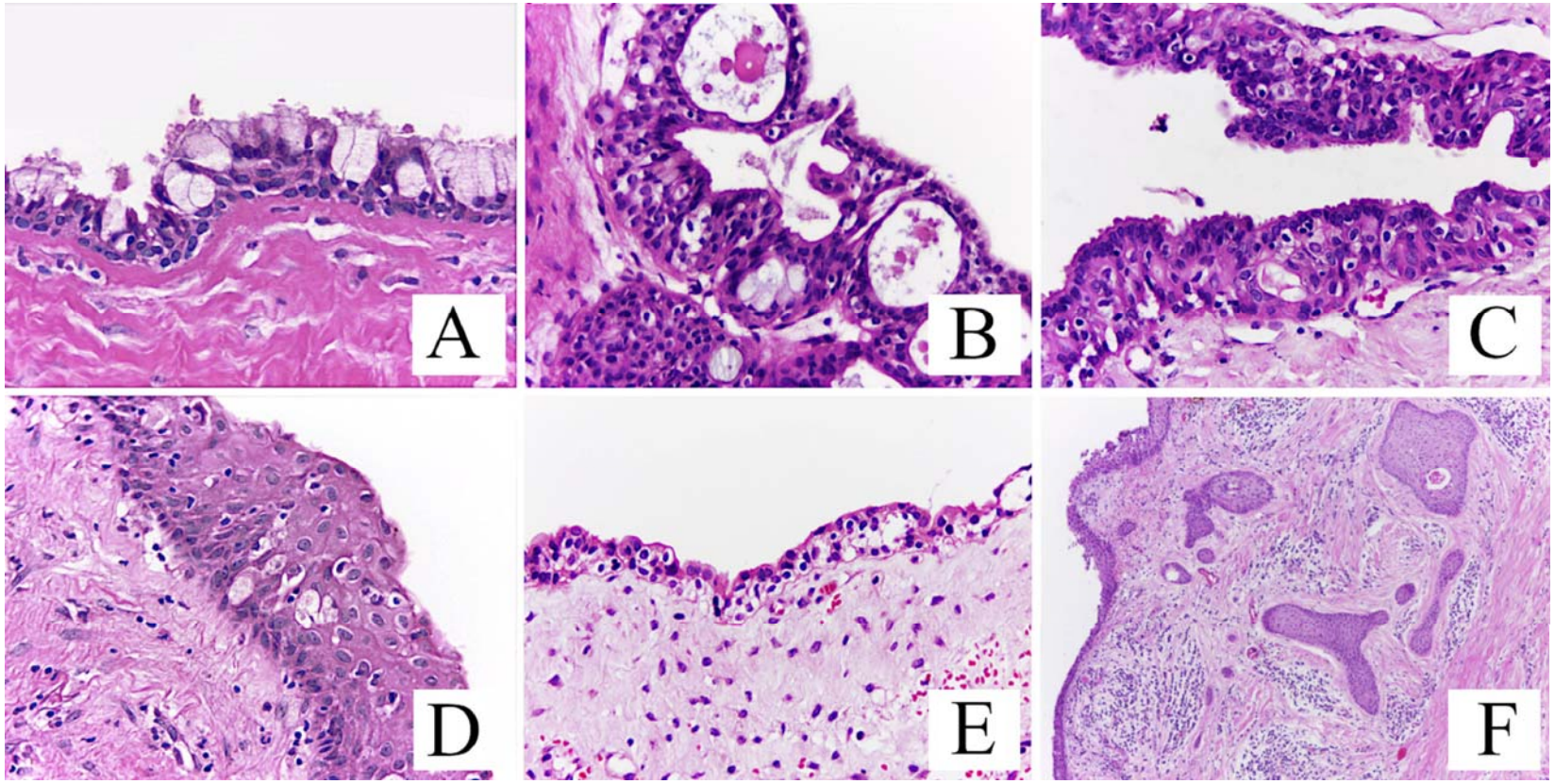

Fig. 1: Typical histological features of the glandular odontogenic cyst. A. Mucous cells with surface cilia (original magnification x 200), B. Intraepithelial microcysts or duct-like structures with surface cilia (original magnification x 400), C. Variable thickness of epithelium with epithelial spherical or whorling patterns (original magnification x 200), D. Clear-cell change in basal cells and superficial cuboidal eosinophilic cells (original magnification x 200), E. Epithelium of variable thickness containing mucous cells and apocrine snouting of luminal cells (original magnification x 200), F. Multiple cystic compartments (original magnification x 100).

radiographic examinations. The radiological differential diagnoses of confirmed GOC cases were also assessed. The radiological features were analyzed by two clinicians, each with more than 5 years experience in the field of Maxillofacial Radiology, with any disagreements resolved by consensus.

Follow-up and recurrence information was recorded when available. The information was analyzed, with emphasis on atypical clinical and radiological presentations, to categorize the clinical spectrum of GOC. Demographic, clinical, and radiologic findings of recurrent cases were tabulated.

All data were entered into a data capture sheet using Microsoft Excel Version 2016 (Microsoft Corporation, Redmond, WA, USA). Parameters were classified as present or absent. To evaluate differences between the categorical variables of different population groups and sex, statistical analysis of the differences between the lesions from South Africa and Brazil was performed using SPSS Software 27.0 (IBM Corporation, Armonk, NY). A univariate frequency table was constructed for each categorical variable, showing the percentage breakdown and distribution of the cases according to the variable parameters. Multivariate tables were thereafter constructed to highlight the interaction between variables, prior to determining the existence of a statistically significant relationship. Lastly, for the purposes of bivariate analysis, the association between two categorical variables was evaluated using the Pearson chi-squared test, with the association between independent categorical and continuous variables evaluated using a two-sample t-test. Correlations with a two-sided asymptotic significance (*P*-value) of less than 0.05 were considered to be statistically significant.

RESULTS

Demographic and clinical features

Table I summarizes the main demographic and clinical features of the 92 cases of GOC included in the study, with analysis of the significance of differences between the cases from South Africa and Brazil. From the 26,256 head and neck cases diagnosed at the South African institution over the study period, 43 cases were confirmed as GOC in our investigation, for an overall prevalence of GOC in the

Table I: Demographic and clinical features of the 92 cases of GOC

Features	**Results (%)**						***P*-value**
	South Africa (n=43)		**Brazil (n=49)**		**Total (n=92)**		
Prevalence	**0.16%**		**0.14%**		**0.15%**		
Mean age, years (range)[1]	46	(22-73)	47	(17-87)	46	(17-87)	0.178
Sex	30M/13F	(2.3:1)	21M/28F	(1:1.3)	51M/41F	(1.2:1)	0.010*
Clinical signs and symptoms[2]	**21**		**39**		**60**		
Asymptomatic swelling	14	(67%)	25	(64%)	39	(65%)	0.843
Painful swelling	5	(24%)	3	(8%)	8	(13%)	0.080
Incidental finding	1	(5%)	10	(26%)	11	(18%)	0.046*
Tooth mobility or paraesthesia	1	(5%)	1	(3%)	2	(3%)	0.655
Mean duration, months (range)[3]	10	(0.5-36)	45	(3-180)	37	(0.5-180)	0.135
Site							
Maxilla	**16**	**(37%)**	**13**	**(27%)**	**29**	**(32%)**	
Anterior and premolar region	7	(44%)	10	(77%)	17	(59%)	0.611
Posterior and molar region	1	(6%)	1	(8%)	2	(7%)	0.926
Anterior and posterior	8	(50%)	2	(15%)	10	(34%)	0.026*
Crosses midline	6	(38%)	3	(23%)	9	(31%)	0.207
Mandible	**27**	**(63%)**	**36**	**(73%)**	**63**	**(68%)**	
Anterior and premolar region	8	(30%)	14	(39%)	22	(35%)	0.263
Posterior and molar region	12	(44%)	12	(33%)	24	(38%)	0.710
Anterior and posterior	7	(26%)	10	(28%)	17	(27%)	0.611
Crosses midline	10	(37%)	20	(56%)	30	(48%)	0.073

[1] Age not reported in 3 South African and 3 Brazilian patients (6 total)

[2] Clinical signs not reported in 22 South African and 10 Brazilian patients (32 total)

[3] The duration was reported in 17 South African and 6 Brazilian patients (23 total)

* A statistically significant relationship exists between the variables at a 95% confidence interval ($p<0.05$)

South African sample of 0.16%. From the 35,709 head and neck lesions diagnosed at the three Brazilian institutions over the study period, 49 cases were confirmed as GOC, resulting in an overall prevalence of GOC in the Brazilian sample was 0.14%. These figures culminated in a total prevalence of GOCs from both countries of 0.15% over the given study period.

The mean age of presentation was 46 years (range 17-87) with a peak incidence in the 4th and 5th decades (Fig. 2). In the overall sample, maxillary lesions presented at a younger age. The overall sample included 51 male and 41 female patients (1.2:1 ratio), demonstrating a strong male predominance in the South African sample (2.3:1), and a slight female predominance in the Brazilian sample (1:1.3). A statistically significant association was found between the two categorical variables of country and sex predilection (P=0.01). Localized swelling was the main clinical presentation, with the majority being asymptomatic (65%), while associated pain was an infrequent finding (13%). Eleven cases were discovered as incidental radiological findings (18%). Painful swelling was usually associated with secondary infection, and although rare, was more frequent in the South African sample (24%) compared to the Brazilian sample (8%). Although this relationship was not statistically significant at the 95% confidence interval (P = 0.08), the geographical differences are noteworthy in the context of further research. Similarly, the discovery of a GOC as an incidental finding was more common among Brazilian patients (26%) when compared to South African patients (5%). This relationship, and geographical difference, proved to be statistically significant (P = 0.046). Tooth mobility and paraesthesia were rarely reported (3%).

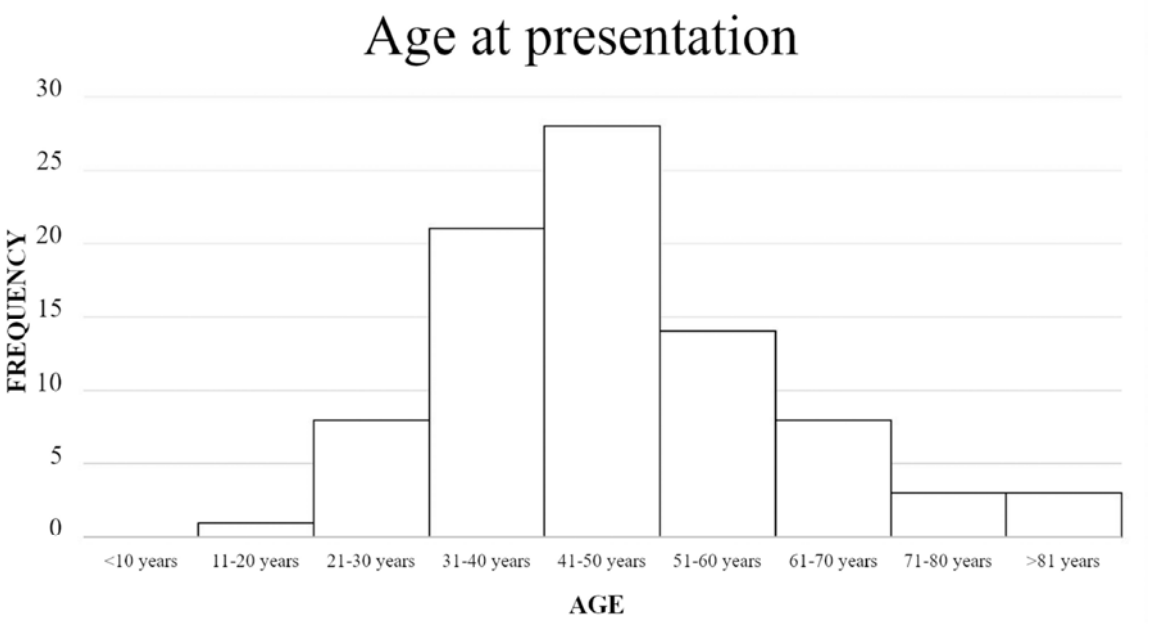

Fig. 2: Age distribution of GOCs included in the study.

The mean duration of the lesion was reported for 23 patients (6 from South Africa and 17 from Brazil). The overall mean duration of the GOCs was 37 months (range 0.5-180 months). The mean duration was shorter in the South African sample (10 months) than among Brazilian patients (45 months), but the difference was not significant (p = .135). GOCs had a mandibular predilection (68% of all cases), of which the posterior and molar regions were most frequently involved, followed by the anterior and premolar regions. Additionally, 6 mandibular cases extended from the posterior and molar region to involve the ramus. Maxillary lesions (32% of all cases) occurred most frequently in the anterior and premolar regions in a so-called "globulomaxillary" relationship (Figure 3). A statistically significant difference between the 2 population groups with regard to frequency of involvement of both anterior and posterior regions in the maxillary cases was found (p = .026), with this pattern being more common in the South African sample. In the overall sample, GOCs had a predilection for the anterior and premolar regions (42%) of the jaws. A total of 39 GOCs (42%) crossed the midline, as seen in 48% of mandibular cases and 31% of maxillary cases. Although mandibular lesions crossing the midline were more common in the Brazilian sample (56%) compared

with the South African sample (37%), no statistically significant relationships relating to geographic differences were found for these lesions ($p \geq .073$).

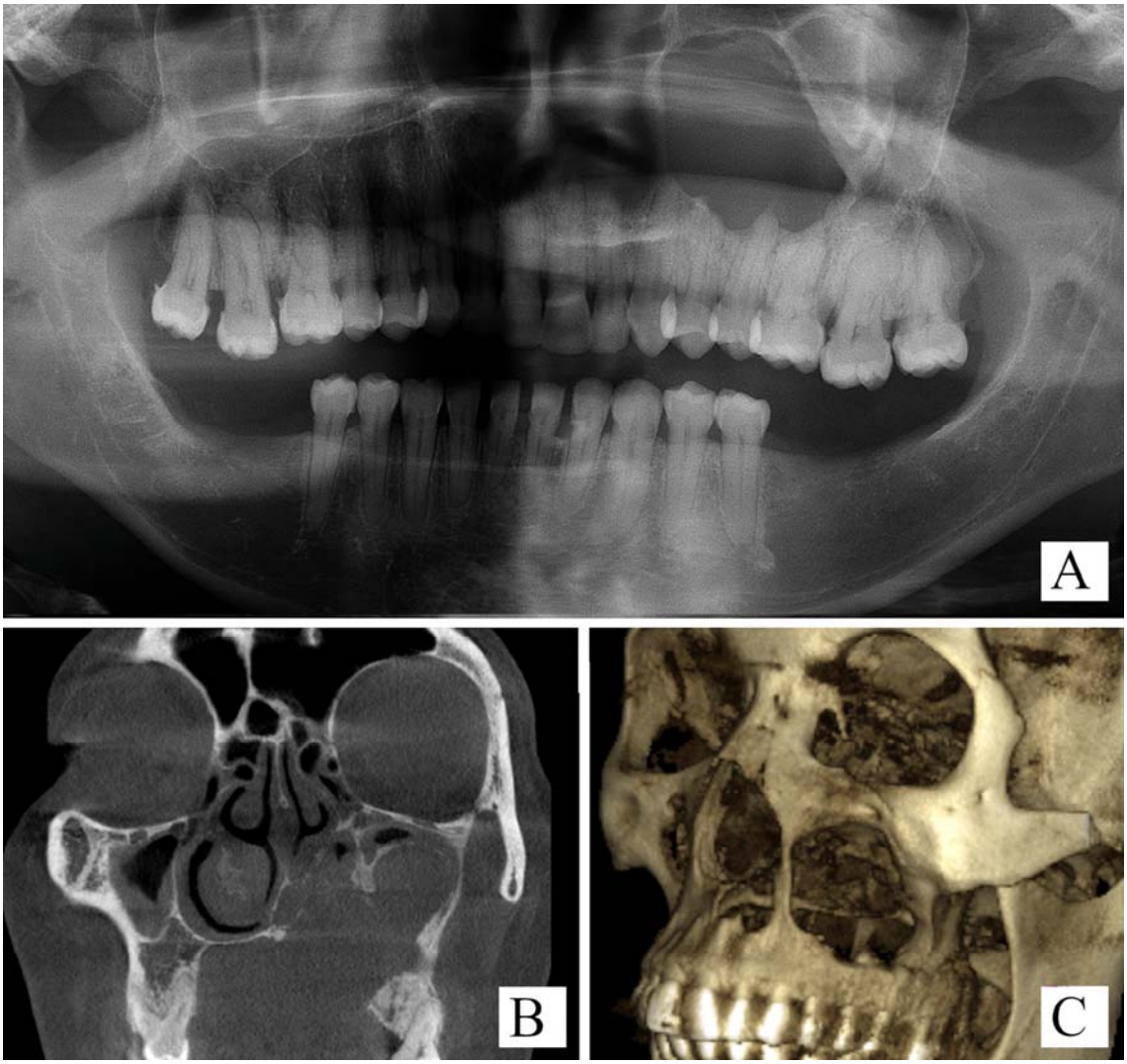

Fig. 3: Maxillary GOC in a 'globulomaxillary' relationship. The panoramic radiograph (A) and the coronal (B) and 3-dimensional (C) reconstructed CBCT images reveal radiological signs of cortical destruction and encroachment into the nasal cavity and maxillary sinus.

Statistical analysis revealed that maxillary GOCs tend to present in younger individuals (mean age = 40 years) compared to those involving the mandible (mean age = 50 years) ($p=0.074$). While not statistically significant at a 95% confidence interval, these findings may be noteworthy in the context

of further research. In both the maxilla and mandible, GOCs extended to involve an average of six teeth, with 12 cases involving 10 teeth or more.

Radiological Features

Radiographic examinations were available for 58 patients, with the features summarized in Table II. For the total sample, intraoral radiographs were available for 8 cases, panoramic radiographs for 51 cases, and CBCT imaging for 17 cases. Well-demarcated borders were seen in the majority of cases (93%), with isolated cases exhibiting a focal loss of demarcation (7%). Thirty-one cases (53%) presented as unilocular lesions and 11 cases (19%) were unilocular with scalloped margins, while 16 cases (28%) exhibited a multilocular appearance (Fig. 4). The majority of cases were uniformly radiolucent (97%), with few cases presenting with specks of internal calcifications (3%).

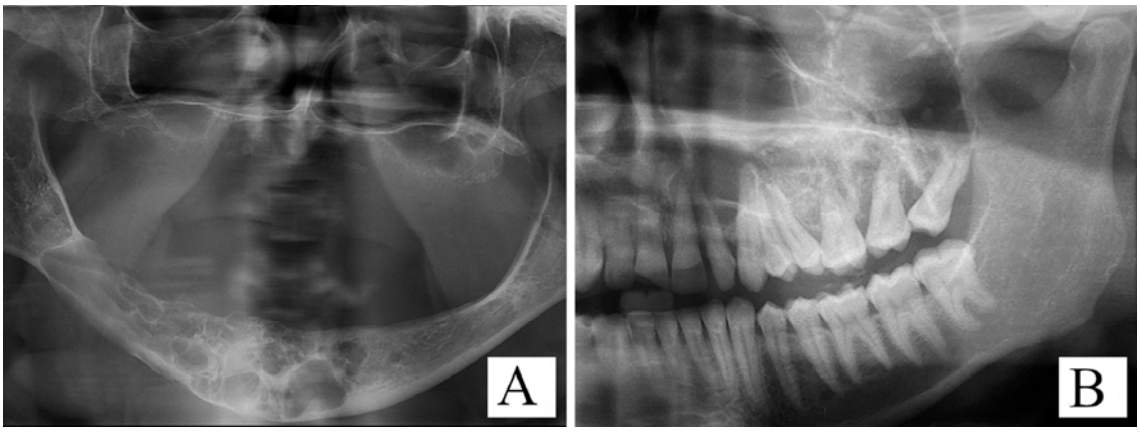

Fig. 4: Multilocular GOCs with specks of internal calcifications. A. GOC in the mandible of an edentulous patient. B. GOC in the posterior maxilla showing radiological signs of cortical destruction as well as maxillary sinus and nasal cavity encroachment.

In cases where teeth were involved, root resorption was the most frequent finding (65%), followed by tooth displacement (33%) and impaction (23%). Within the Brazilian sample, root resorption was more common (77%) compared to the South African sample (50%). The relationship between these variables, however, was not deemed to be statistically significant (p=0.097). Cases whereby impacted

Table II: Radiological features of the 92 cases of GOC

Features	Results (%)						*P*-value
	South Africa (n=24)		Brazil (n=34)		Total (n=58)		
Borders							
Well-demarcated	22	(92%)	32	(94%)	54	(93%)	0.717
Poorly-demarcated	2	(8%)	2	(6%)	4	(7%)	0.717
Locularity							
Unilocular	15	(63%)	16	(47%)	31	(53%)	0.246
Unilocular with scalloped margins	4	(17%)	7	(21%)	11	(19%)	0.708
Multilocular	5	(21%)	11	(32%)	16	(28%)	0.334
Radiodensity							
Radiolucent	23	(96%)	33	(97%)	56	(97%)	0.801
Internal calcifications	1	(4%)	1	(3%)	2	(3%)	0.801
Effects on surrounding structures							
Root resorption[3]	11/22	(50%)	23/30	(77%)	34/52	(65%)	0.097
Tooth displacement[3]	7/22	(32%)	10/30	(33%)	17/52	(33%)	0.984
Tooth impaction[3]	6/22	(27%)	6/30	(20%)	12/52	(23%)	0.496
Cortical expansion	14	(58%)	22	(65%)	36	(62%)	0.622
Cortical thinning	5	(21%)	14	(41%)	19	(33%)	0.104
Cortical destruction	11	(46%)	11	(32%)	22	(38%)	0.297
Scalloping between roots	6	(25%)	15	(44%)	21	(36%)	0.136
Maxillary sinus encroachment[4]	7/10	(70%)	5/8	(63%)	12/18	(67%)	0.181
Nasal cavity encroachment[4]	8/10	(80%)	5/8	(63%)	13/18	(72%)	0.094
Inferior alveolar nerve displacement[5]	8/14	(57%)	8/26	(31%)	16/40	(40%)	0.411
Differential diagnosis							
GOC[6]	1	(4%)	7	(21%)	8	(14%)	0.221
Odontogenic keratocyst	6	(25%)	7	(21%)	13	(22%)	0.692
Radicular cyst[6]	3	(13%)	8	(24%)	11	(19%)	0.333

Ameloblastoma[6]	5	(21%)	5	(15%)	10	(17%)	0.498
Nasopalatine duct cyst[6]	3	(13%)	3	(9%)	6	(10%)	0.684
Dentigerous cyst[6]	3	(13%)	3	(9%)	6	(10%)	0.684
Other[7]	3	(13%)	1	(3%)	4	(7%)	0.717

[3] GOCs affected edentulous areas in 2 South African and 4 Brazilian patients

[4] Incidence was calculated for maxillary lesions only

[5] Incidence was calculated for mandibular lesions only

[6] Certain observation totals were lower than the expected count of 5, impacting on the meaningfulness of the Chi-squared P-value. The Fisher's exact test has been computed, and shown in the table, for a more accurate reflection of the P-value of this variable

[7] Other radiological differential diagnoses included odontogenic myxoma, antral mucocele, and surgical ciliated cyst

teeth were seen in association with the cyst predominately involved third molars (67%). Interestingly, two cases were associated with supernumerary teeth and one with an odontoma (Fig. 5).

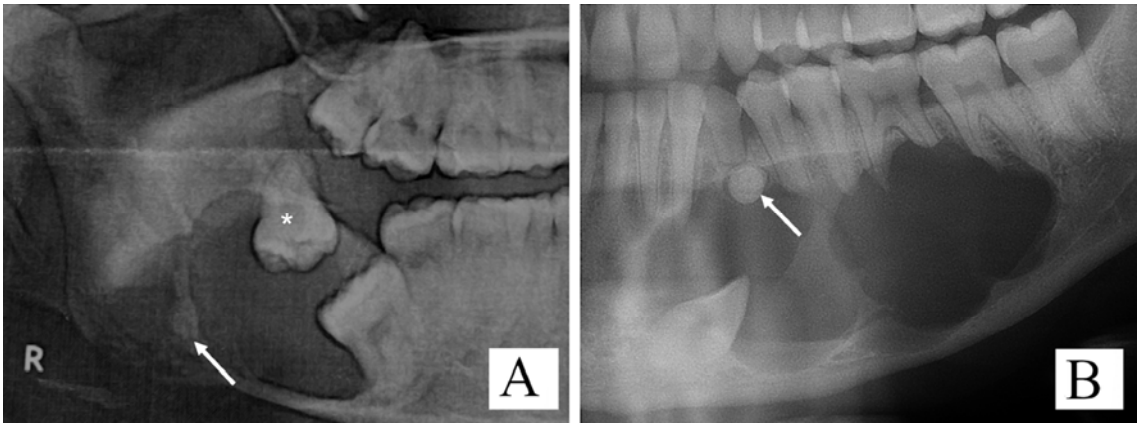

Fig. 5: Rare findings in GOCs. A. Panoramic radiograph of a posterior mandibular GOC associated with a distomolar (asterisk) and an associated calcified structure (arrow). D. Multilocular GOC associated with an impacted left mandibular canine and an odontoma (arrow).

Cortical expansion was seen in 62% of cases. Loss of cortical integrity was common (71%), either via cortical thinning (33%) or cortical destruction (38%). Scalloping between the roots was seen in more than a third of cases (36%). Displacement of anatomical structures was a common finding, with maxillary sinus and nasal cavity encroachment seen in 67% and 72% of maxillary lesions, respectively. Among mandibular lesions, 40% of GOCs resulted in displacement of the inferior alveolar canal.

GOCs with the typical characteristic radiological presentation of well-demarcated uni- or multilocular lesions in the anterior mandible, crossing the midline or in a ‘globulomaxillary’ presentation, were seen only in 14% of cases. In many instances, GOCs were radiologically indistinguishable from other entities, resembling odontogenic keratocysts, radicular cysts, or ameloblastomas in 22%, 19% and 17% of cases, respectively. Rarer radiological differential diagnoses included nasopalatine duct cysts (10%), dentigerous cysts (10%), and other entities (7%).

Table III: Recurrent cases

Case	**1**	**2**	**3**	**4**	**5**
Age/Sex	34/F	60/M	55/M	44/F	63/F
Location	Mandibular posterior	Mandibular anterior and posterior	Mandibular anterior	Mandibular anterior	Mandibular anterior
Treatment	Multiple enucleation procedures	Marsupialisation	Not reported	Multiple enucleation procedures	Not reported
Period of recurrence (years)	5	5	4	20	5
Change in radiological presentation	Increase in size WD → PD UL → ML Increased expansion with cortical destruction	Increase in size Cortical destruction	Increase in size UL → ML Increased expansion with cortical destruction	Increase in size UL → ML	Increase in size

F: Female, M: Male, WD: Well-demarcated, PD: Poorly-demarcated, UL: Unilocular, ML: Multilocular

Follow-up information was available for 5 cases that recurred (Table III), with each case showing progressively more destructive radiological features. In all recurrent cases an increase in size from the initial presentation was noted (Fig. 6). In a single case, the margins of the lesion changed from well- to poorly-demarcated. Three cases progressed from an initial unilocular radiolucency to a multilocular appearance.

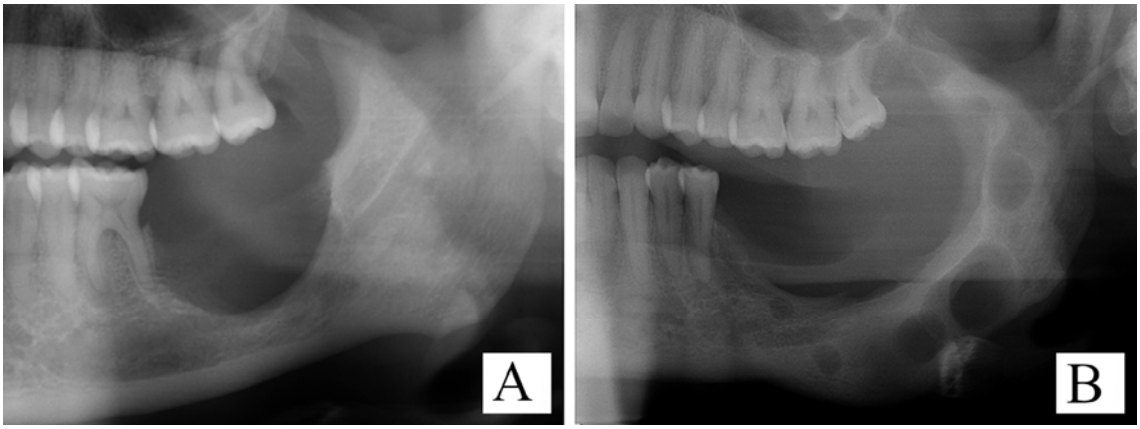

Fig 6: Recurrent GOC. A. Post-operative panoramic radiograph following surgical enucleation. B. Recurrence after five years showing progression in size with a multilocular appearance and bony expansion.

DISCUSSION

GOC is a relatively uncommon entity, representing only 0.2% of all odontogenic cysts.[17] Fewer than 250 cases have been reported in the literature[3,5,18–20], with the largest single study sample comprising 46 cases.[4] To the authors' knowledge, the current study represents the largest sample size reported in a single study, excluding reviews of the literature. In the current sample, GOCs represented only 0.15% of all head and neck lesions diagnosed from four institutions, emphasizing the rarity of these cysts. Due to suboptimal specimens or inconclusive histological criteria, 20 cases originally diagnosed as GOC were excluded from the study following review. This highlights the need for adequate tissue samples to render a definitive and accurate diagnosis.

GOCs frequently affect patients during the 5th to 7th decades of life (mean age of 48 years), with most cases presenting after 30 years of age.[3,4,7,9,16] The mean age of presentation of the current sample

corresponds to this range, with only eight cases in our sample occurring in patients younger than 30 years. No confirmed cases of GOC have been reported in the first decade;[16] the youngest reported patient was an 11-year-old male with a lesion in the anterior mandible.[21] Additionally, three GOCs in the current study arose in patients over the age of 80 years, which is a rare finding.[3] GOCs show an almost equal sex distribution, with a slight male predilection.[3,4] This was reflected in the current study, except for a strong male predominance noted in the South African sample. These population differences have previously been reported[15], and may reflect the specific sex distribution in different population groups. In the overall sample, maxillary lesions were diagnosed and treated in younger patients, possibly related to the thin cortical bone exhibiting earlier expansion.

GOCs typically present as asymptomatic swellings or may be discovered incidentally upon radiographic examination.[4,15] This emphasizes the need for comprehensive and systematic review of radiographs. These initial clinical presentations were mirrored in the current study, in which 65% were asymptomatic and 18% were incidental findings. Isolated cases presenting with pain and paraesthesia have been reported in the literature.[4,22] Pain was more frequently associated with cases from the South African sample, usually in conjunction with secondary infection. Paraesthesia and tooth mobility were noted as initial presenting signs only in one case each, pointing to the rarity of these findings.[4,22,23] The published literature may have underreported the clinical duration of GOCs, possibly due to an imprecise recollection of the initial presentation. The reported mean duration in the current sample was 37 months. A shorter duration was seen among South African cases, possibly due to a higher percentage of patients presenting with associated pain.

GOCs have a predilection for the anterior regions of the jaws, in particular the mandible, with a tendency to cross the midline.[3,4,6,9,23] This corresponds to the findings of the current study where 42% of the total sample was located in the anterior and premolar regions and 42% of cases crossed the midline. In a review of the literature, 36% of GOCs were located in the anterior/premolar region of the mandible.[3] The mandible was more commonly involved in the current sample, but with the posterior and molar region as the most frequently involved mandibular subsite. In the current study,

six GOCs extended from the mandibular molar region to involve the ramus, findings which have been previously reported.[3,6,7] However, 27% of the cases in the present investigation involved both the anterior and posterior mandibular regions. This finding was also reported in 24% of reviewed GOC cases[3], indicating that GOCs can reach a considerable size. When the maxilla is affected, GOCs tend to occur in the canine region in a "globulomaxillary" relationship.[4,6,7] This correlated with the findings of the current study, in which 59% of maxillary cysts occurred in the anterior and premolar region. A statistically significant difference was noted for this subsite, which was more common in the South African cases ($P = 0.026$). Both population groups included large numbers of mandibular cysts crossing the midline. This pattern was more common in the Brazilian sample.

The typical radiological features of GOCs include well-demarcated uni- or multilocular radiolucencies affecting the anterior mandible, often crossing the midline.[15] The borders of GOCs appear well-demarcated; however, rare cases with poorly-demarcated borders have been reported.[7,16] Poorly-demarcated borders were rarely seen in the current sample, possibly in lesions affected by chronic inflammation. Radiologically, GOCs present as unilocular or, less often, multilocular radiolucencies with some reports showing similar frequencies of uni- and multilocularity.[3,6,7,9,16] Additionally, unilocular lesions with scalloped borders have been reported, although rarely.[7,16] Unilocular lesions were more frequently observed in the current sample, with 72% of cases being either unilocular or unilocular with scalloped margins. Maxillary GOCs are often unilocular, although multilocular variants have been reported[6,7], as was seen in three maxillary lesions (10%) in the current sample. On average GOCs reach a size of 5 cm, with multilocular variants being slightly larger.[6,7] Exuberant lesions, reaching a size of up to 16.5 cm, have been reported in the literature.[6] The current sample included large lesions involving up to 14 teeth, with 12 cases involving 10 or more teeth. Unfortunately, due to different magnification factors between different radiographic units and different imaging modalities, accurate estimations of size could not be determined.

GOCs frequently present as radiolucent lesions, although rare cases containing small foci of internal calcifications have been reported.[3,7] Four cases in the current sample were seen in association

with dystrophic calcifications and reactive bone formation on histologic examination. To the authors' knowledge, this has not been reported previously in the literature. In 2 of these cases, the internal calcifications were not identified radiologically, possibly due to the small size of the calcified structures

Tooth displacement, although rare, is more commonly seen compared to root resorption.[3,6,7] This is in contrast to the current findings in which root resorption was frequently seen and was especially prevalent in the Brazilian sample. This could be due to the longer clinical duration of the GOCs. Impactions were the least reported effect on surrounding teeth. Due to the timing of occurrence, it is not surprising that the associated impacted teeth are frequently third molars.[15] To the authors' knowledge, this study included the first reported cases of GOCs associated with supernumerary teeth. Occasionally, GOCs have been documented in association with ameloblastomas, florid cemento-osseous dysplasias, and metaplastic cartilage.[19,20,24] In a single South African patient, the lesion presented with an associated odontoma, an uncommon feature reported only once in the literature.[18]

Cortical expansion associated with GOCs is a common radiological finding[3] and was present in a large number of cases in the current study. In a review of the literature, 86% of GOCs resulted in either cortical thinning or perforation, pointing to the aggressive potential of the lesions.[16] In the current research a loss of cortical integrity, manifested as thinning and destruction, was noted in 71% of cases. Cortical expansion and thinning were more common in the Brazilian sample, but cortical destruction occurred more frequently in cases from South Africa. The findings of tooth displacement, root resorption, and cortical perforation in the current study were significantly higher than reported in the literature review by Chrcanovic et al.[3] Furthermore, previous radiological studies of GOCs have not reported on the displacement of anatomical structures.[6,7,15] In the current study, anatomic displacement was very frequent and slightly also more common in the South African sample. GOCs resulting in encroachment of the maxillary sinus and nasal cavity have been reported.[15] These effects were frequently seen in the maxillary lesions included in the current sample. The effects on surrounding structures, along with the higher frequency of cortical destruction, associated pain and

shorter clinical duration, may point to a more aggressive presentation in the South African sample.

The radiological differential diagnosis for GOC may include odontogenic keratocyst, radicular cyst, ameloblastoma, nasopalatine duct cyst, and dentigerous cyst. GOCs seen in association with non-vital teeth have been reported previously mimicking a radicular cyst radiologically.[15] Macdonald-Jankowski commented that the radiological distinction between GOC and radicular, nasopalatine duct, and dentigerous cysts can be made with ease.[15] However, in this study, GOCs were radiologically indistinguishable from the more common differential diagnoses in a number of cases. In the majority of lesions, GOCs presented radiologically with a similar appearance to OKCs, especially in cases extending into the ramus. The association with non-vital teeth also resulted in a significant number of GOCs being mistaken radiologically for radicular cysts. In 17% of cases, GOCs presented with radiological features resembling that of ameloblastoma, a benign odontogenic neoplasm with aggressive clinical behavior. The high frequency of anterior maxillary cases showing a propensity to cross the midline often results in nasopalatine duct cysts entering the radiological differential diagnosis. Lastly, 10% of cases had a dentigerous presentation. This clinical presentation, paired with the similar histological features of metaplastic dentigerous cysts, highlights the importance of using established diagnostic criteria in reaching a diagnosis of GOC, as described by Fowler et al.[4]

Due to the retrospective nature of this study, information regarding recurrence was only available for five cases and an estimate on the recurrence rate in this sample was not possible. Recurrence was frequently associated with a change in radiological appearance, with recurrent lesions presenting with a more aggressive clinical course. This raises the question of whether the more aggressive presentation of recurrent cases could be linked to recurrent GOCs acquiring a *MAML2* gene rearrangement. *MAML2* testing was not performed in all recurrent cases to substantiate this hypothesis, which is a limitation of the current study. The clinical distinction between GOCs and central MECs may not be straightforward, as the mean age of presentation and sex distribution of these entities are similar.[3,14,25] The initial statement made on the clinical distinction between these two lesions, based on the presence of pain, associated impacted teeth, and a posterior location, cannot be

regarded as completely accurate considering the findings of the current investigation. Although the majority of central MECs present as asymptomatic swellings, they have increased frequencies of reported pain and paraesthesia compared to GOCs.[25] Additionally, central MECs appear to occur more commonly in the maxilla, in contrast to GOCs.

CONCLUSION

GOCs typically present as asymptomatic swellings frequently involving the mandible, usually affecting patients during the 5th to 7th decades of life. They may present with a wide spectrum of clinical and radiological features, ranging from cysts with typical GOC-like presentations to more aggressive lesions. Most cases in the current study presented as well-defined unilocular radiolucent lesions. Cortical expansion and loss of cortical integrity either via thinning or destruction were common findings. When the maxilla is involved, maxillary sinus and nasal encroachment is common. The academic debate around whether GOC falls under the spectrum of central MEC or represents a precursor of this tumor needs further substantiation, but for now cannot be disregarded. Clinical signs of pain and paraesthesia seem to be important features in distinguishing GOCs from central MECs. The radiological signs seem less reliable, as many GOCs may show aggressive and atypical radiological presentations. The need for advanced imaging for the surgical planning of lesions exhibiting radiological signs of aggression, including cortical destruction, is justified based on the reported high recurrence rate of GOCs.

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