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Retrospective Study

Contrast enhanced multidetector computed tomography features and histogram analysis can differentiate ameloblastomas from central giant cell granulomas

Adarsh Ghosh, Meyyappan Lakshmanan, Smita Manchanda, Ashu Seith Bhalla, Prem Kumar, Ongkila Bhutia, Asit Ranjan Mridha

Abstract

BACKGROUND

No qualitative or quantitative analysis of contrast enhanced CT images has been reported for the differentiation between ameloblastomas and Central Giant Cell Granulomas

AIM

To describe differentiating multidetector computed tomography (MDCT) features in central giant cell granulomas (CGCG) *vs* ameloblastomas and to compare the differences in the enhancement of these two lesions qualitatively and using histogram analysis.

METHODS

MDCTs of CGCGs and ameloblastomas were retrospectively reviewed to evaluate qualitative imaging descriptors. Histogram analysis was used to compare the extent of enhancement of the soft tissue. Fisher's exact tests and Mann-Whitney-U test were used for statistical analysis.(p-value < 0.05).

RESULTS

Twelve CGCGs and 33 ameloblastomas were reviewed. Ameloblastomas had a predilection for the posterior mandible with none of the CGCGs involving the angle. CGCGs were multilocular (58.3%), with a mixed lytic sclerotic appearance(75%). Soft tissue component was present in 91% of CGCGs, which showed hyperenhancement (compared to surrounding muscles) in 50%, while the remaining showed iso-enhancement. Matrix mineralization was present in 83.3% of cases. On the other hand, Ameloblastomas presented as a unilocular(66.7%), lytic(60.6%) mass with solid component present in 81.8% of the cases. However, the solid component showed iso-enhancement in 63%. No matrix mineralization was present in 69.7% of cases. Quantitatively, the enhancement of soft tissue in CGCG was significantly higher than in ameloblastoma on histogram analysis (p <0.05), with a minimum enhancement of > 49.05 HU in the tumour providing 100% sensitivity and 85% specificity in identifying a CGCG.

CONCLUSION

A multilocular, lytic sclerotic lesion with significant hyperenhancing soft tissue component, which spares the angle of the mandible and has matrix mineralization, should direct one to a prospective diagnosis of CGCG.

INTRODUCTION

The most current World Health Organisation classification of jaw tumours places giant cell granulomas under "giant cell lesions and simple bone cyst". These include both central and peripheral giant cell granulomas(1). Central giant cell granuloma (CGCG) usually appears as an expansile, multiloculated lesion with post-contrast enhancement and soft tissue extension(2–4). Histologically it is characterized by focally distributed giant cells, spindle cells and possible areas of haemorrhage. A similar radiological and histopathological appearance may also be seen in brown tumours of hyperparathyroidism, and further clinical and laboratory correlation is required

whenever aggressive, atypical or multiple CGCGs are seen(1,5). CGCGs are slow-growing and insidious, though, increased rates of growth, presence of pain, tooth resorption or cortical erosions are considered signs of aggressive behaviour(2,3,6). CGCGs are relatively rare and tend to occur with a female preponderance in the second decade of life. Accelerated growth during pregnancy or following child-birth suggests hormone responsiveness of CGCGs. Though the exact pathophysiology of the tumour is yet to be elucidated: a reparative response to trauma, haemorrhagic products and inflammation is presumed to result in tumorigenesis. The classical lytic multilocular appearance of CGCGs on radiographs makes their differentiation from ameloblastomas, odontogenic cyst, aneurysmal bone cysts, and odontogenic fibromas difficult(3,7). This differentiation is, however, vital because CGCGs are treated less aggressively [curettage, intralesional interferon, steroids or calcitonin injections(8)] as compared to other lesions with a similar radiological appearance. Ameloblastomas are by far is the most prevalent odontogenic tumour in the developing world(9), constituting about 14% of all jaw lesions(10). Though benign; ameloblastomas exhibit an aggressive growth pattern, with up to 70% of cases (11) undergoing malignant transformation. It presents most frequently in males, in their third to fifth decades of life, as a slowly progressive swelling. The lesion favours the posterior mandible (63.15% of all cases as per one study(12)) and on imaging is a close differential of CGCGs with its unilocular or multilocular, lytic, expansive appearance(13). Ameloblastomas are treated more radically and aggressively [with block resection, radiation therapy, vemurafenib(14)] vis-à-vis CGCGs making differentiation between the two crucial clinically.

Contrast enhanced CT imaging can help characterise tumour biology better than non-contrast scans(15). Although tumour location, appearance, contour and mass effect of the lesion on surrounding structures and teeth can be easily evaluated on non-contrast multi detector computed tomography (MDCT) (4,7,16,17)or on cone beam CT (CBCT), the presence of enhancing soft tissue and the extent of enhancement in the tumour can provide significant insight into tumour biology and can differentiate tumour types and pathological processes. For example contrast enhanced CT scans helps

differentiate purely cystic lesions of the jaw from cyst like lesions(18), a task relatively difficult on non-contrast MDCT scans or on CBCTs. Similarly contrast enhanced dynamic MDCT can help differentiate ameloblastomas (19)from other cystic jaw lesions including keratocystic odontogenic tumours. Further quantification of the extent of tumour enhancement using histogram and texture analysis(20) can also characterise these tumours. However to our knowledge no qualitative or quantitative analysis of contrast enhanced CT images has been reported for the differentiation between ameloblastomas and Central Giant Cell Granulomas (CGCGs)

Given this background, we undertook this study to compare the MDCT features of CGCGs and ameloblastomas. More specifically we compared the utility of quantitative and qualitative evaluation of extent of tumour enhancement in differentiation of these two tumours.

MATERIALS AND METHODS

Subjects

The electronic records available with the department of pathology were searched, to identify cases of CGCGs and ameloblastomas, between December 2016 to January 2019. All cases with multidetector CT (MDCT) were included in the study: Six patients who did not have MDCT were thus excluded. A total of 12 CGCGs and 33 ameloblastomas(n-45) were identified and used in this study. The study was approved by the institutional ethics committee vide Ref No: IEC-622/03.07.2020,RP-31/2020.

Imaging Technique

All MDCT acquisitions were performed either on a 64-MDCT scanner (Siemens SOMATOM Sensation, Erlangen Germany) or 128-MDCT scanner (Siemens SOMATOM Definition Flash, Erlangen Germany) available with our department. The images were acquired using 120 kV with automated tube current modulation, and a quality reference mAs of 80. A slice thickness of 0.6mm was used. A 16-cm Field of View, 512 × 512 matrix, was used to reconstruct data with routine 1mm sections being obtained using

standard soft tissue and bone window kernels. Contrast-enhanced CT (CECT) images were available for 38 of these 45 scans. Amongst these 38, venous phase images acquired at 60-70 s after intravenous injection, was available in 35 patients (8-CGCG, 27 ameloblastoma) [1-1.5 mL/kg of non-ionic iodinated contrast (Iohexol 350 mg of iodine/mL)]. Only arterial phase images were available as part of a head neck angiography protocol in three patients. Non-contrast MDCT was available in 7 patients.

Imaging Interpretation

Two radiologists (SM and M with 16- and 6-years' experience in head neck imaging, respectively) blinded to clinical and pathologic data reviewed all the MDCT scans in consensus. Non-consensus was resolved by reviewing with a third radiologist (ASB). Zone wise mapping of each lesion (45) was done, as explained in **figure 1**. Location of the lesion (mandible or maxilla), density (mixed, lytic or sclerotic as characterized on the bone window), multilocularity (unilocular with 1 or 2 thin septae; multilocular, honeycombing pattern); presence or absence of solid component and erosion or thinning of the surrounding cortex was recorded. In mandibular lesions, the involvement of the angle (yes/ no), and the status of the inferior alveolar canal was recorded (involvement/ erosion) as well. The status of the overlying teeth (missing or root resorbed/ present/ adjoining roots displaced); adjacent fat stranding and muscle thickening (present or absent) were noted. Venous phase images were evaluated ($n = 35$) to quantify the amount of soft tissue in each lesion (0-<10%; 10-25%; 25-50%; 50-75%; >75%) and the type of enhancement of the solid component in the lesion was also characterized (purely cystic; hypo-enhancing; iso-enhancing; hyper-enhancing- the enhancement in these cases was compared to that of the surrounding muscles). Mineralization of the tumour was recorded (absent; mineralized osteoid; thin bony septa; thick septa with associated matrix). The three largest diameters of each lesion were recorded (along and perpendicular to the axis of mandible; craniocaudal). These

measurements were then used to derive the lesion's volume using the volume formula for an ellipsoid (0.523xAPxTRxCC).

Quantitative analysis of enhancement

The venous phase MDCT images were evaluated to compare the degree of enhancement between the tumours. Specifically, the contrast-enhanced MDCT images were opened on 3D Slicer 4.11.0 (https://download.slicer.org/). A freehand oval ROI measuring atleast 1cm in diameter was drawn on the largest bulk of the tumour, ensuring that the ROI was placed on soft tissue only avoiding bony septa (Supplementary Figure 1). This was done by AG with six years' experience in head neck imaging and ROI placement was reviewed by SM. The pyRadiomics plugin (https://pyradiomics.readthedocs.io/en/Latest/index. html) was then used to evaluate the histogram of the distribution of the Hounsfield units(HU) in the ROIs. Specifically skewness; uniformity; entropy; kurtosis; mean, median, maximum, minimum, 10th and 90thpercentiles of the HU values in the histogram was evaluated. Purely cystic lesions (*n* = 6) were excluded from this analysis.

Statistical analysis

All data were tabulated and tested for normality when indicated. Continuous data were compared between the two data sets using the Mann-Whitney-U test, while Fisher's exact test was used to compare categorical data. A p value<0.05 was considered statistically significant. Receiver operating characteristic (ROC) curve analysis was used to obtain the area under the curve (AUC) for texture parameters found to be significantly different between the two groups; optimal cut-offs were obtained using bootstrapped Youden index. A leave-one-out cross-validation of the various enhancement parameters was done to evaluate generalizability.

RESULTS

A total of 12 CGCGs and 33 ameloblastomas were included in our study. The median age patients with ameloblastoma were higher [35years(95%CI of median 28– 48years] as compared to patients with CGCG [29years (95%CI of median 18–42years)], this, however, was not statistically significant (p-value= 0.26). Of the patients having ameloblastomas 27.30%(n = 9) were females, and 72.70% (n = 24) were males. The prevalence of CGCGs was nearly equal between both the sexes: 41.70% (n = 5) in females vs 58.30% (n = 7) in males. This difference was again not statistically significant.

Location.

Both the pathologies favoured the mandible, with five ameloblastoma and 4 CGCG appearing in the maxilla. CGCGs favoured a more central location with six lesions being located in zone 1(50.00%), 3 in zone two (25.00%) and two lesions in zone 3(16.70%)(table 1 and figure1). Only a single CGCG was large enough to involve zone 1,2 and 3 simultaneously. This was significantly (p<0.0001) different from ameloblastomas which had a more varied distribution. Fourteen (42.40%) ameloblastomas were located exclusively in zone 3. Simultaneously, 9 ameloblastomas were large enough to involve all three zones and 2 amongst these were large enough to cross the midline. Fifty per cent (n = 14 out of 28) of ameloblastomas had involvement of the angle of the mandible. In contrast, none of the CGCGs had this feature (p-value =0.013).

Volume and size

Lesion volume was determined using the ellipsoid formula. CGCGs were significantly lower in volume (median volume =10.31cc) as compared to ameloblastomas (median volume 35.9cc) – p-value 0.027 (table 2). ROC curve analysis and the associated cut off is provided in table 3. While there was considerable overlap between the two entities' volumes, a cut-off of ≤13.04cc obtained 84.85% (68.1 - 94.9)specificity in identifying a CGCG. Similarly, the diameter of ameloblastomas [measured along the long axis of the mandible] was higher than that of CGCGs with a cut off of ≤3.5cm (95%CI ≤2.1cm to

≤4.4cm) providing 50% (95%C.I. 21.1 - 78.9) sensitivity and 90.91% (95%C.I 75.7 - 98.1) specificity in identifying the latter.

Lesion appearance on bone window

60.6% of ameloblastomas were purely lytic (n = 20), as compared to only 25% of CGCGs (n = 3) (p-value =0.047). A majority of all CGCGs – 75% (n = 9) were predominantly mixed in appearance with both lytic and sclerotic components being present in the lesion. However, only 39.4% of ameloblastomas were mixed in appearance (n = 13). Neither of the tumours was purely sclerotic. Ameloblastomas (n = 22) were predominantly unilocular [66.7%] compared to 58.3% of CGCGs, which were multilocular. Matrix mineralization either in the form of osteoid, thin septa, or thick septa and associated dense matrix, was more common in CGCGs than ameloblastoma, where 70% showed no matrix mineralization.

Qualitative evaluation of contrast enhancement

Evaluation of the degree of enhancement of solid component on venous phase images (n = 35, 8-CGCG, 27 ameloblastoma) showed that six ameloblastomas were purely cystic with no solid component, and 17(62.9%) ameloblastomas showed enhancement which was similar to the surrounding muscles. In comparison, 4(50%) CGCGs showed enhancement higher than the surrounding muscles. This was significantly different (p-value = 0.013) from ameloblastomas, with only one ameloblastoma (3.7%) showing enhancement higher than muscles. These above findings are summarised in table 1 and figure 2

Quantitative evaluation of enhancement.

Histogram analysis (n = 29, 8-CGCG, 21 ameloblastoma) of the enhancement of the solid component in the venous phase image was carried out after excluding the purely cystic lesions(n = 6). CGCG had higher minimum, median, mean and maximum enhancement as compared to ameloblastomas(p<0.05) on venous imaging (Table 2). A bootstrapped ROC curve analysis provided the AUC of the individual parameters as

well as the optimum cut-offs. Minimum enhancement of >49.0538, had a sensitivity of 100% and a specificity of 85.71% in identifying a CGCC over ameloblastoma. The cut-offs, their associated sensitivity and specificity, and accuracy metrics of a leave-one-out cross-validation are provided in table 3.

DISCUSSION

We described the MDCT imaging features of CGCGs and contrasted them with ameloblastomas. Morphologically, both CGCGs and ameloblastomas had several overlapping features – making their differentiation difficult. Both ameloblastomas and CGCGs can be either unilocular or multilocular. Cortical expansion, cortical perforation, root displacement and root resorption are features suggestive of an aggressive variant of CGCG; however, these features are also present in ameloblastomas. MDCT or cone-beam CT (CBCT) is preferred over radiography because it allows better evaluation of the bony anatomy, especially the integrity of the buccal and lingual cortex. Further MDCT with intravenous contrast allows better evaluation of the soft tissue component in these lesions. Location wise, we found that though the CGCGs favoured the central jaw, up to 25% of the lesions were also found in the ramus(22,23). Because of the relatively small size of CGCGs, only one lesion was large enough to involve all the three zones. Ameloblastomas because of their larger sizes tended to involve more than one zone, with the most predominant preference for zone 3 (the ramus of the mandible). This varied distribution is similar to that described in the literature (14,15); involvement of the angle when present was highly specific for ameloblastoma. None of the CGCGs demonstrated the involvement of the angle. CGCGs were considerably smaller(28.82±40.75cc) in volume as compared to ameloblastomas (66.18±84.33cc) [Table 2 and 3]. Ameloblastomas are locally aggressive tumours, while CGCGs are slow-growing insidious masses which are sometimes known to regress spontaneously. Thus the smaller volume of CGCG may be keeping with the natural history of CGCGs [table 2]. Cortical expansion, cortical perforation, root displacement and root resorption like previously stated, can occur in both the tumours(19,24–26). Even in our series, there

was no difference in the prevalence of root resorption, tooth displacement, cortical expansion or cortical perforation between the two entities (table 1). CGCGs were predominantly multilocular(58.3%) with a unilocular appearance in only 25% of cases. In contrast, 67% of ameloblastomas were unilocular.75% of CGCGs showed both sclerotic and lytic components on the bone window(75%), while 60% of ameloblastomas had a predominant lytic appearance (figure 2 and 3) . Additionally, the presence of osteoid either in the form of a mineralized matrix, thin bony septa or thick bony septa with dense mineralized matrix was a significant feature: present in 83% of CGCGs. In comparison, 70% of ameloblastomas had no mineralization. Imaging feature of ameloblastomas as contrasted with CGCGs is present in table 4 and figures 2 and 3. Solid soft tissue was present in more than 90% of all CGCGs, while 18% of ameloblastomas were purely lytic. The solid component of CGCGs showed avid enhancement in 50% of cases, while in the rest it showed enhancement similar to surrounding muscles, and only 4% of ameloblastomas showed hyperenhancement. On quantitative evaluation, we found that the solid components in CGCGs enhanced significantly greater than the solid tissue in ameloblastomas. Nackos *et al*(4) in their case series of 7 CGCGs had described that the soft tissue in all the CGCGs showed avid contrast enhancement. Similarly, in our series, 50% of CGCGs showed enhancement greater than surrounding muscles, while rest showed a similar enhancement. While a mathematical discussion of each of the parameters used is beyond this paper's scope, briefly, entropy characterizes the randomness of the distribution of the HU values in the ROI. Skewness quantifies the asymmetry in the distribution of the HU values; meanwhile, kurtosis measures the histogram's peakedness obtained from the HU values. A more detailed description can be read in the excellent review by Lubner *et al* (21). Histogram analysis showed that the mean, minimum, and maximum enhancement of CGCGs was significantly higher than ameloblastomas(table 2 and 3). A cut off of >49.05 HU for minimum enhancement in the tumour allowed 100% (63.1 - 100.0) sensitivity and 85.71% (63.7 - 97.0) specificity in differentiating CGCG from ameloblastoma.

The difference in enhancement patterns may be explained based on microvascular density(MVD) of these two tumours. While there are no studies directly comparing MVD of these two entities, separate studies have shown that ameloblastomas had an MVD of 14.9 ± 6 (27) compared to 24.5±5.8 in CGCGs(28). This difference, we hypothesize would result in a faster and a more considerable peak enhancement of CGCGs than ameloblastomas, which would then translate to differences in the maximum and minimum venous phase-contrast enhancement of CGCGs. OPG and CBCT only evaluate the morphology of tumours. Tumour vascularity, enhancement and MVD are important components of radiological tumour assessment and can be well evaluated using contrast-enhanced MDCTs. Since in an index case, morphological imaging feature may overlap, the marked differences in enhancement may allow a confident prospective distinction between CGCGs and ameloblastomas.

CGCGs are rare tumours of the jaw making their prospective diagnosis difficult. The classical lytic multilocular appearance of CGCGs on radiographs makes their differentiation from odontogenic cyst, aneurysmal bone cysts, odontogenic fibromas and ameloblastomas(3,7) [the most prevalent odontogenic tumour in the developing world (9)] difficult. However, this differentiation is vital because CGCGs are treated less aggressively [curettage, intralesional interferon, steroids or calcitonin injections(8)] compared to other lesions with a similar radiological appearance. We believe this is the unique value of our study, demonstrating the utility of contrast enhanced CECT. We acknowledge that imaging alone cannot distinguish these lesions from their other mimics, including giant cell tumours and aneurysmal bone cysts. Moreover, because CGCGs are rare, prospective radiological diagnosis is often difficult and histopathological correlation is thus needed of a definitive diagnosis. Sometimes, however, a pathological diagnosis may not be forthcoming(29), and in such cases, the radiological-pathology correlation becomes essential. We believe our findings would add value in such complex cases. Moreover, in patients due to multiple concurrent CGCGs(30) in patients with a mutation of the RAS/MAPK pathway(31), or underlying systemic illnesses, not all lesions undergo biopsy. In such patients, imaging would be

valuable in follow up and diagnosis. We believe contrast enhanced MDCT would be invaluable in work up and management of such cases.

This study has several potential limitations. Of a broad potential range of lytic lesions of the jaw, we have compared only ameloblastomas *vs* CGCGs in this study. In our routine practise, we have seen that ameloblastomas have several overlapping imaging features with CGCGs. This compounded with the rarity of CGCGs makes their prospective identification difficult. Given the rarity of CGCGs, we decided to contrast the imaging and enhancement characteristics of CGCGs with its most common mimic in the jaw. The retrospective design of the study, with an asymmetric dataset, might have prevented the demonstration of more variations in the imaging features of CGCGs. Because of these limitations, further prospective studies are required to investigate the imaging characteristics and enhancement features of CGCGs, ameloblastomas and their various mimics.

CONCLUSION
In conclusion, significant hyperenhancement of the soft tissue component on CECT in a jaw tumour may allow a prospective diagnosis of CGCGs, especially in a multilocular lytic sclerotic centrally located jaw tumour with matrix mineralization.

ARTICLE HIGHLIGHTS
Research background
To evaluate the contrast enhanced Multi-detector Computed tomography features of ameloblastomas and central giant cell granulomas

Research motivation
To evaluate the contrast enhanced Multi-detector Computed tomography features of ameloblastomas and central giant cell granulomas

Research objectives

To describe differentiating multidetector computed tomography (MDCT) features in central giant cell granulomas (CGCG) *vs* ameloblastomas and to compare the differences in the enhancement of these two lesions qualitatively and using histogram analysis.

Research methods

MDCTs of CGCGs and ameloblastomas were retrospectively reviewed to evaluate qualitative imaging descriptors. Histogram analysis was used to compare the extent of enhancement of the soft tissue. Fisher's exact tests and Mann-Whitney-U test were used for statistical analysis.(p-value < 0.05).

Research results

Twelve CGCGs and 33 ameloblastomas were reviewed. Ameloblastomas had a predilection for the posterior mandible with none of the CGCGs involving the angle. CGCGs were multilocular (58.3%), with a mixed lytic sclerotic appearance(75%). Soft tissue component was present in 91% of CGCGs, which showed hyperenhancement (compared to surrounding muscles) in 50%, while the remaining showed iso-enhancement. Matrix mineralization was present in 83.3% of cases. On the other hand, Ameloblastomas presented as a unilocular(66.7%), lytic(60.6%) mass with solid component present in 81.8% of the cases. However, the solid component showed iso-enhancement in 63%. No matrix mineralization was present in 69.7% of cases. Quantitatively, the enhancement of soft tissue in CGCG was significantly higher than in ameloblastoma on histogram analysis (p <0.05), with a minimum enhancement of > 49.05 HU in the tumour providing 100% sensitivity and 85% specificity in identifying a CGCG.

Research conclusions

A multilocular, lytic sclerotic lesion with significant hyperenhancing soft tissue component, which spares the angle of the mandible and has matrix mineralization, should direct one to a prospective diagnosis of CGCG.

Research perspectives

Future direction can evaluate the role of perfusion imaging differentiating these two tumor types

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PRIMARY SOURCES

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