Unicystic ameloblastoma with stromal giant cells: A case series of a rare entity

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ABSTRACT

Ameloblastoma is a locally aggressive, benign epithelial odontogenic neoplasm currently classified to include conventional, unicystic and extraosseous/peripheral subtypes. Giant cells have been reported in various malignancies, but rarely in odontogenic neoplasms. To date, only a single case of unicystic ameloblastoma with stromal giant cells has been reported in the literature. We report two new cases with histological features compatible with unicystic ameloblastoma with stromal giant cells. CD68 immunohistochemical staining of the giant cells supported a histiocytic origin. Further research is needed to better understand the origin and nature of these giant cells.

Keywords: Odontogenic tumour; Ameloblastoma; Multinucleated giant cells; Immunohistochemistry

INTRODUCTION

Ameloblastoma is a benign epithelial odontogenic neoplasm with aggressive behaviour characterised by expansion and a tendency for local recurrence if incompletely excised.[1, 2] In the current classification of benign odontogenic tumours, ameloblastomas are divided to include ameloblastoma (often termed conventional ameloblastoma), unicystic ameloblastoma and extraosseous/peripheral subtypes.[3-5]

Multinucleated giant cells are well documented in various malignancies, but have rarely been described in odontogenic neoplasms.[6, 7] To date only a single case of unicystic ameloblastoma with stromal giant cells has been reported in the literature.[6] We report two new cases with histological features compatible with unicystic ameloblastoma with stromal giant cells. Additionally, this article summarises the relevant literature pertaining to this rare finding in unicystic ameloblastomas, highlighting the nature and possible histogenesis of these giant cells.

CASE 1

A 39-year-old female patient presented with an asymptomatic cystic lesion in the right posterior mandible noted on routine radiographic examination. The panoramic radiograph demonstrated a well-circumscribed radiolucency between the right mandibular second premolar and first molar teeth with associated root resorption of the premolar tooth (Figure 1). The clinical suspicion was that of a radicular cyst. The lesion was completely excised and submitted for histological assessment.

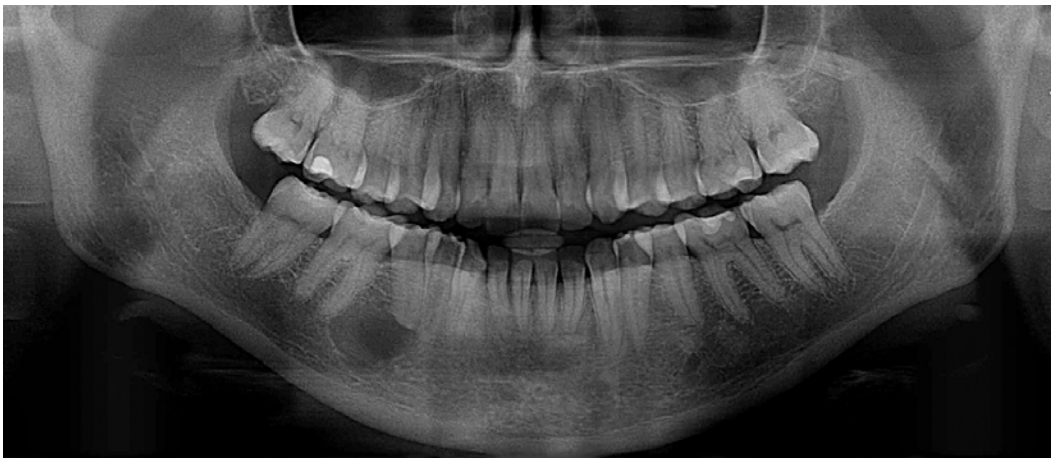

Fig. 1. Panoramic radiograph showing a well-circumscribed radiolucency between the right mandibular second premolar and first molar teeth.

The specimen submitted consisted of an intact cystic lesion measuring 10x8mm, with a wall thickness of approximately 1mm. Histological evaluation confirmed the presence of a cystic lesion lined by an ameloblastomatous epithelium. This epithelium was characterised by columnar cells showing a hyperchromatic, polarised basal cell layer (Figure 2A). The superficial aspect of the epithelial lining appeared loosely cohesive resembling the stellate reticulum. The wall of the cystic lesion consisted of dense fibrous connective tissue containing numerous multinucleated giant cells (Figure 2B). There was no evidence of epithelial proliferation into the lumen or cyst wall. A CD68 immunohistochemical stain showed positivity in the giant cells, suggesting a histiocytic origin (Figure 3). The overall radiological and histological features supported a diagnosis of unicystic ameloblastoma, with the rare addition of stromal giant cells. The patient is currently under close follow-up with no signs of recurrence after 18 months.

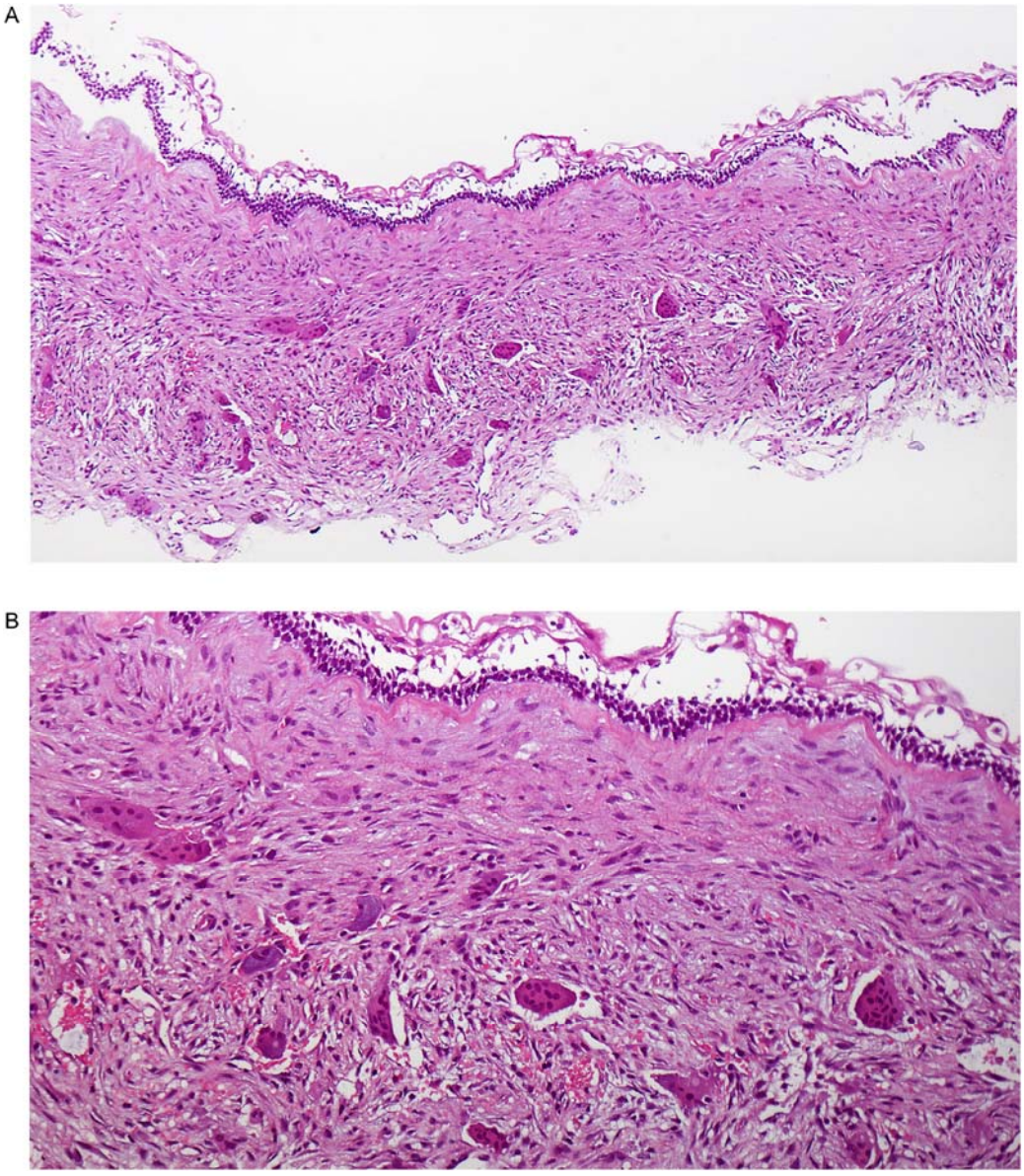

Fig. 2. (A) Hematoxylin and eosin (H&E)-stained section showing the cystic lesion lined by an ameloblastomatous-type epithelium (original magnification x 40). (B) A high-power H&E-stained section showing numerous multinucleated giant cells in the wall of the cystic lesion (original magnification x 100). A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM06310.

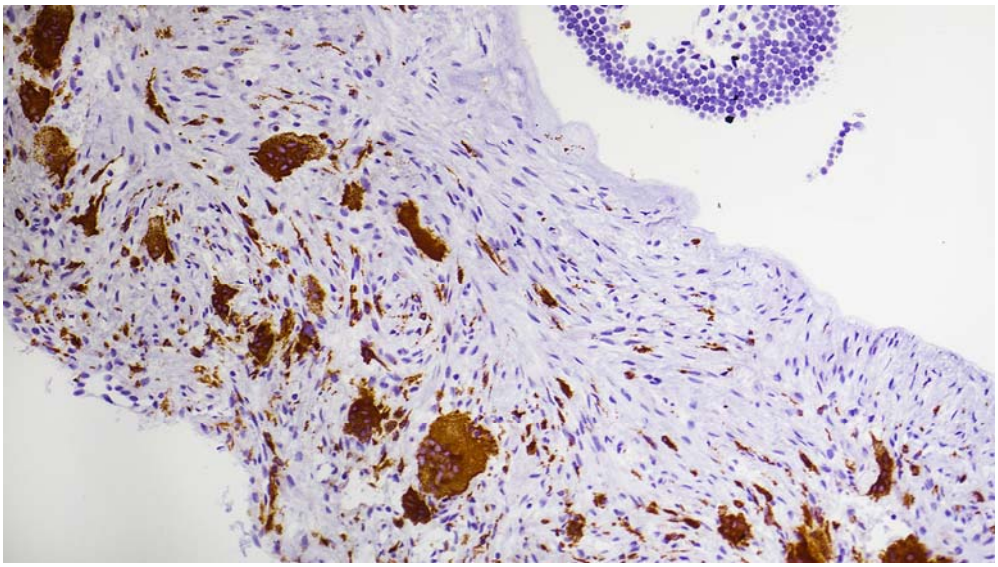

Fig. 3. A CD68 immunohistochemical stain showing positivity in the multinucleated giant cells (original magnification x 100).

CASE 2

A 6-year-old female patient presented with an asymptomatic swelling involving the left posterior mandible. The panoramic radiograph demonstrated a well-circumscribed radiolucency involving the crown of an unerupted mandibular second molar tooth with associated root resorption of the mandibular first molar (Figure 4). The clinical suspicion was that of a dentigerous cyst or an ameloblastoma. An incisional was performed and submitted for histological assessment.

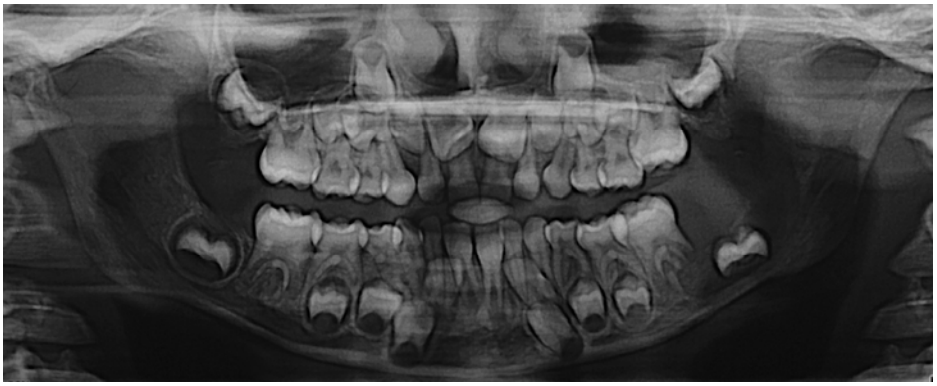

Fig. 4. Panoramic radiograph showing a well-circumscribed radiolucency involving the crown of an unerupted mandibular second premolar with root resorption of the mandibular first molar.

Histological evaluation showed a cystic lesion lined by an ameloblastomatous epithelium, which led to a diagnosis of ameloblastoma. The patient then underwent complete surgical removal of the tumour. The specimen submitted consisted of a large, surgically opened cystic lining measuring 26x12mm, with a wall thickness ranging between 1-3mm. Histological evaluation of the surgical specimen showed a large cystic cavity lined by an ameloblastomatous epithelium. The basal layer consisted of columnar to cuboidal cells with hyperchromatic nuclei exhibiting reverse polarity. The superficial layer of the epithelium consisted of loosely arranged epithelial cells resembling the stellate reticulum of the enamel organ. The wall of the cystic lesion consisted of dense fibrous connective tissue with a mixed chronic inflammatory infiltrate of moderate intensity and haemorrhagic foci. In addition, scattered neoplastic islands of ameloblastomatous epithelium infiltrated the wall of the cystic tumour. Finally, numerous multinucleated giant cells were also observed in many regions of the cyst wall (Figure 5). These giant cells were found both peripherally, but also adjacent to the epithelial component of the tumour. Similar to Case 1, a CD68 immunohistochemical stain showed positivity in the giant cells, suggesting a histiocytic origin (Figure 6). The overall radiological and histological features supported a diagnosis of unicystic ameloblastoma with stromal giant cells. The patient is currently under close follow-up with no signs of recurrence after 12 months.

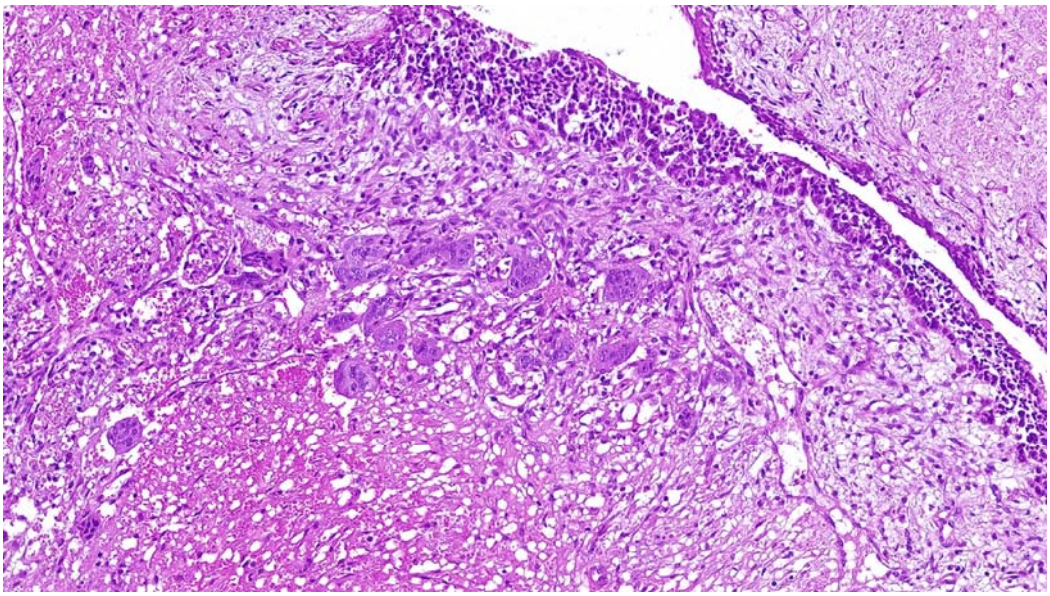

Fig. 5. A high-power H&E-stained section showing numerous multinucleated giant cells in the wall of the cystic lesion (original magnification x 100). A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM06311.

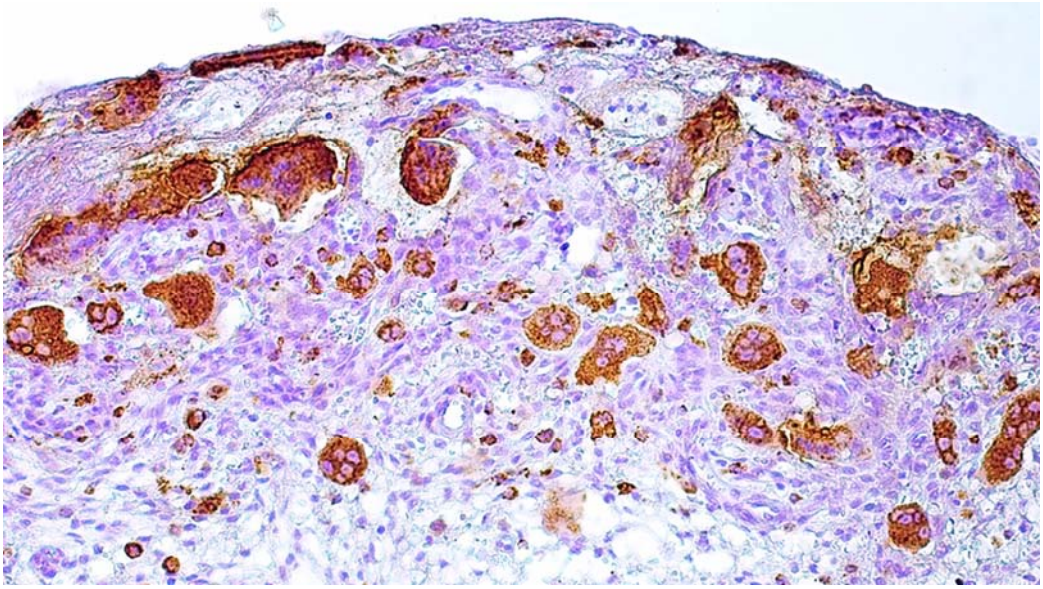

Fig. 6. A CD68 immunohistochemical stain showing positivity in the multinucleated giant cells (original magnification x 100).

DISCUSSION

Ameloblastoma is a locally aggressive, benign epithelial odontogenic neoplasm with a strong mandibular predilection characterised by expansion and a tendency for local recurrence if incompletely excised.[1, 2] In the 2005 World Health Organization classification of benign odontogenic tumours, ameloblastomas were divided into solid/multicystic, unicystic, desmoplastic and extraosseous/peripheral subtypes.[8] Currently, the classification has been simplified to only include ameloblastoma (often termed conventional ameloblastoma), unicystic ameloblastoma and extraosseous/peripheral types.[3-5] Desmoplastic ameloblastoma has been reclassified as a histologic subtype and not a separate entity.[5]

Conventional ameloblastomas have no gender predilection and occur most commonly in the fourth and fifth decades of life.[3] Radiographically, they present as multilocular radiolucencies, in some instances causing root resorption of adjacent teeth. Two main histological patterns are recognised, follicular and plexiform, although this does not influence tumour behaviour or patient management.[1, 4] The follicular pattern is characterised by islands of odontogenic epithelium within a mature fibrous stroma. The cells at the periphery of the islands are columnar and often show palisading. The central portions resemble the stellate reticulum and in some instances show cystic change.[1] Several variants of follicular ameloblastoma exist, including acanthomatous, granular, spindle cell and basal cell/basaloid. The plexiform pattern consists of odontogenic epithelium arranged in anastomosing cords. In both histologic types, pleomorphism and mitotic activity are rare findings.[1] Several studies have reported activating mutations in the mitogen-activated protein kinase (MAPK) and Hedgehog signalling pathways in the pathogenesis of ameloblastomas.[2, 5] According to

cytogenetic studies, the most common mutation is *BRAF V600E*, ranging from 43% to 82%.[2, 5] Other MAPK-related mutations, include the RAS family (*KRAS, HRAS, NRAS*) and *FGFR2*, showing a combined incidence of only 28%.[2, 5] *SMO* mutations form part of the Hedgehog pathway and have an incidence of 22%[5]. Interestingly, the molecular profile of ameloblastomas is strikingly different between the maxilla and mandible.[2] Ameloblastomas with *SMO* mutations are predominantly found in the maxilla (57%), while those with *BRAF V600E* mutations are mainly located in the mandible (75%).[5]

Unicystic ameloblastoma comprises 10% of all ameloblastomas, presenting as a single cyst. Approximately 90% occur in the posterior mandible associated with an unerupted third molar.[1] The mean age is 16 years for those associated with an impacted tooth, and 35 years in the absence of an impaction.[3] Radiographically, it presents as a corticated, unilocular radiolucency, which may be pericoronal. Importantly, unicystic ameloblastomas should only be provisionally diagnosed on an incisional biopsy, even if radiology suggests a unilocular lesion.[1] The final diagnosis should be confirmed following histological examination of the enucleation specimen. Histologically, three variants have been described. The luminal variant shows a simple cyst lined by ameloblastomatous epithelium with no proliferation into the lumen or cyst wall. The intraluminal variant is characterised by intraluminal extensions of the lining epithelium, without tumour infiltration into the surrounding fibrous wall.[1, 3] These two types are considered to have a good prognosis, rarely recurring even after simple enucleation.[4] Finally, the mural variant shows an epithelial proliferation into the wall of the cyst in a plexiform or follicular pattern.[1, 3] Recent evidence suggests that the mural type behaves more aggressively, and should therefore be classified as a conventional ameloblastoma and treated as such.[3, 4]

Mutational status of *BRAF V600E* and *SMO* has been examined in a small number of unicystic ameloblastomas. In total, 73% were found to bear the *BRAF V600E* mutation, while none showed mutations in *SMO*.[2, 5]

The presence of giant cells has been documented in malignancies of the breast, thyroid and uterus.[6, 7] The origin and nature of these giant cells are still incompletely understood. However, the current consensus is that there are two types of giant cells associated with neoplasms, neoplastic and non-neoplastic.[7] Giant cell-rich lesions confined to the jawbones include central giant cell granuloma and cherubism. Other giant cell-rich lesions showing a predilection for this region include aneurysmal bone cysts and brown tumour of hyperparathyroidism.[9]

Giant cells are exceedingly rare in odontogenic neoplasms, with only isolated reports in benign odontogenic entities. Central odontogenic fibromas (COdF) may in rare instances show an associated giant cell lesion (GCL).[10] Histologically, the tumour consists of a classic COdF component with an adjacent GCL. Importantly, these two components are not intimately admixed, and authors are uncertain whether the GCL represents a reactive phenomenon, forms part of the histological spectrum of the entity, or equates to true hybrid tumour.[10, 11] Eversole noted the lack of association between other odontogenic neoplasms and GCLs, disagreeing with the suggestion of a reactive phenomenon.[10] A recent multicentric study of COdFs postulated that tumour contains unique periodontal stem cells capable of differentiating into osteoclast-like multinucleated giant cells.[11]

Boss first reported three cases of giant cells in ameloblastomas in 1964.[12] This article suggested that the giant cells were reactive stromal cells and further subdivided them into three types, namely foreign-body giant cells, giant cells as an integral component of a reparative granulomatous process, and osteoclasts resorbing newly formed bone spicules in the connective tissue. The giant cells in two of the cases in this original article were considered to be part of a reactive process, whereby the stroma was transformed into reparative granulomatous tissue secondary to bone damage by the ameloblastoma.[12] The giant cells in the third case were considered as osteoclastic activity in response to bone destruction. Kawakami *et al* argued that determining the origin of these giant cells was impossible on routine hematoxylin and eosin-stained sections alone.[7, 13] In their study, the giant cells showed strong acid phosphatase activity, but were negative to lysozyme and alpha-1 antitrypsin. Ultrastructurally, the cytoplasm of the giant cells contained numerous mitochondria with a comparatively smooth cell membrane. These findings supported origin from histiocytic mononuclear cells in response to bone invasion by the ameloblastoma.[7] Richard *et al* showed that the osteoclast-like giant cells in their case were in response to the woven bone seen in the fibrous stroma surrounding the ameloblastoma.[13] Immunohistochemical staining showed that all giant cells expressed CD45 (leukocyte common antigen) and CD68, but were negative for cytokeratin intermediate filaments. Additionally, both the giant cells in the stroma surrounding the tumour and those associated with areas of focal osteoid formation expressed HLA-DR. The giant cells on the surface of mineralized bone were negative for HLA-DR.[13] This immunophenotype confirmed origin from macrophage polykaryons rather than osteoclasts. The only case of unicystic ameloblastoma with stromal giant cells was reported by Muni Sekhar *et al* in 2015.[6] Immunohistochemical analysis to determine the origin of the giant cells showed

similar results to those of Richard *et al*. The authors concluded by stating that the presence of giant cells in close proximity to the tumour may indicate that these giant cells form part of a foreign body giant cell response.[6]

CONCLUSION

Evidence of giant cells in benign neoplasms is rare, with only isolated reports in benign odontogenic tumours. To the author's knowledge, these cases represent only the second and third examples of unicystic ameloblastoma with features of multinucleated giant cells in the stroma reported in the literature. Further research is needed to better understand the origin and nature of these giant cells.

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