



Aggressive granular cell ameloblastoma arising from radicular cyst: a case report of an unusual variant and a public health concern

Abhishek Banerjee^{1,2}, Sisca Meida Wati², Moumalini Das³, Kumar Chandan Srivastava^{4,5},
Deepti Shrivastava⁶, Vincenzo Ronsivalle⁷, Rocco Franco⁸, Marco Cicciù⁷, Giuseppe Minervini^{9,10}

¹Department of Oral and Maxillofacial Pathology, Awadh Dental College and Hospital, Jamshedpur, India; ²Department of Oral and Maxillofacial Pathology, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia; ³Department of Oral Pathology, Awadh Dental College & Hospital, Jamshedpur, India; ⁴Division of Oral Medicine & Radiology, Department of Oral & Maxillofacial Surgery & Diagnostic Sciences, College of Dentistry, Jouf University, Sakaka, Saudi Arabia; ⁵Department of Oral Medicine and Radiology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, India; ⁶Division of Periodontics, Department of Preventive Dental Sciences, College of Dentistry, Jouf University, Sakaka, Saudi Arabia; ⁷Department of General Surgery and Surgical-Medical Specialties, School of Dentistry, University of Catania, Catania, Italy; ⁸Department of Biomedicine and Prevention, University of Rome “Tor Vergata”, Rome, Italy; ⁹Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai, Tamil Nadu, India; ¹⁰Multidisciplinary Department of Medical-Surgical and Odontostomatological Specialties, University of Campania “Luigi Vanvitelli”, Naples, Italy

Contributions: (I) Conception and design: A Banerjee, SM Wati, KC Srivastava; (II) Administrative support: A Banerjee, KC Srivastava; (III) Provision of study materials or patients: A Banerjee, M Das, V Ronsivalle, G Minervini; (IV) Collection and assembly of data: A Banerjee, SM Wati, KC Srivastava; (V) Data analysis and interpretation: A Banerjee, M Das, M Cicciù, R Franco, G Minervini; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Dr. Abhishek Banerjee, BDS, MDS, PhD-P. Associate Professor, Department of Oral and Maxillofacial Pathology, Awadh Dental College and Hospital, NH-33, Danga, P.O. Bhilaipahar, Jamshedpur, Jharkhand 831012, India; Department of Oral and Maxillofacial Pathology, Faculty of Dental Medicine, Universitas Airlangga, Surabaya, Indonesia. Email: abhishek.banerjee376@gmail.com; Dr. Kumar Chandan Srivastava, BDS, MDS, PhD, MBA, PGDBS, PGDCR, MHScPH, MFD RSCI, MFDS RCPS (Glasg), MFDS RCSEdMDTFEd. Division of Oral Medicine & Radiology, Department of Oral & Maxillofacial Surgery & Diagnostic Sciences, College of Dentistry, Jouf University, King Khalid Road, Dist. Al Matar, Sakaka 72345, Al-Jouf Province, Saudi Arabia; Department of Oral Medicine and Radiology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai 602105, India. Email: drkcs.omr@gmail.com.

Background: Ameloblastoma is the second most common odontogenic tumor and categorized into various clinical and histopathological types. They are found exclusively in the mandibular posterior region, mainly between third and fifth decades of age. However, granular cell ameloblastoma is a unique and rare histologic variant of unicystic/multicystic ameloblastoma. Although it is rare, it has greater recurrence potential and chances of malignant potential.

Case Description: A 75-year-old male patient reported to a dental clinic with a slow growing swelling in the right side of posterior jaw region in the last 7 months. On questioning, he revealed a history of radicular cyst enucleation in the same region almost 3 years back. On intraoral examination, the swelling seems originating from #46 region and extended posteriorly to involve retromolar area. Furthermore, a purulent discharge was observed on compression along with bicortical expansion. A straw-colored fluid was withdrawn from the swelling. Panoramic and cone beam computed tomography (CBCT) examination revealed a homogenous, multilocular radiolucent lesion with bicortical expansion. Later, histopathological examination displayed features of a granular cell ameloblastoma. The paper describes the clinical presentation, radiographic and histopathologic features along with the treatment. Additionally, rarity of the case is discussed while comparing it with previously reported cases of ameloblastoma arising from the radicular cyst.

Conclusions: Clinical, radiographic and histopathological combined interpretation is essential in every case of oral pathology for final diagnosis. Immunohistochemistry is important in many aspects to rule out behavioral changes in the pathological entity.

Keywords: Case report; ameloblastoma; mandible; radicular cyst

Received: 02 October 2023; Accepted: 05 March 2024; Published online: 18 March 2024.

doi: 10.21037/jphe-23-114

View this article at: <https://dx.doi.org/10.21037/jphe-23-114>

Introduction

Background

Ameloblastoma is considered to be second most common of all odontogenic tumor (11%) which can be clinically subdivided into solid, unicystic, peripheral, and desmoplastic (1). The latter is considered as an aggressive tumor. Histologically, ameloblastoma are further divided into types like granular, follicular, basal cell, acanthomatous, and desmoplastic (1). Ameloblastoma are exclusively found in the mandible or lower jaw, near the angle area and mostly found between the third and fifth decades (2). Ameloblastoma affecting middle aged adults in posterior part of the mandible shows peculiar honeycomb or soap-bubble appearance especially in multilocular lesions (3). Ameloblastoma with a granular cell pattern is a unique histologic subdivision of unicystic/multicystic ameloblastoma. It is rare and accounts for about 3–5% in occurrence. Clinically or radiographically, this granular cell

ameloblastoma looks like other ameloblastoma but one can appreciate its unique features only in histopathology (1,4–6). It has features such as it has granular changes in stellate reticulum like cells which is present inside the follicles of the epithelium. The clusters of granular cells have full of cytoplasm with eosinophilic granules filled in them. The granular cells are there in the central mass of the epithelial tumour islands, cords. The island's periphery is formed of columnar cells which are non-granular (4). Cytoplasmic overload is the reason behind the granularity according to the studies. It may also be due to ageing or degenerative changes in cases of lesions that are long-standing. Krompecher in 1918 at first had seen and described this tumour, when it was termed as pseudo-xanthomatous cells. Granular cell ameloblastoma has an aggressive behaviour having high chances of recurrence, particularly after inadequate surgical management and may forward to metastasis (2). Therefore, post operative follow up is very necessary. Radicular cysts are common phenomenon with teeth having necrotic pulp.

Highlight box

Key findings

- Interesting case of a rare occurrence of granular cell ameloblastoma.
- Based on the history and previous surgical experience, the lesion was diagnosed as radicular cyst.
- Occurrence of granular cell ameloblastoma in the site of previously diagnosed site of radicular cyst signifies the role of differentiation of odontogenic cells.

What is known and what is new?

- Numerous reports on unicystic ameloblastoma arising from radicular cyst have been reported, but granular cell ameloblastoma occurrence of rare.
- This manuscript adds information about the significance of differentiating odontogenic cells and its possibilities of forming new lesions.

What is the implication, and what should change now?

- An innocuous appearing lesion such as radicular cyst should be evaluated diligently and its differential diagnosis should include rarities such as granular cell ameloblastoma.

Rationale and knowledge gap

Although rare, but in some cases, there is higher potential of radicular cyst turning out into ameloblastoma according to literature (7,8). Most of the case reports depicted the development of unicystic ameloblastoma from radicular cyst; however, the occurrence of other solid variants of ameloblastoma has been least discovered or reported.

Objective

This paper aims to report a case of an aggressive granular cell ameloblastoma which is arising from a pre-operated radicular cyst and therefore describes its rarity and uniqueness in detecting the case with its radiographic and histopathologic findings and subsequent treatment. We present this article in accordance with the CARE reporting checklist (available at <https://jphe.amegroups.com/article/view/10.21037/jphe-23-114/rc>).



Figure 1 Extraoral and intraoral clinical findings. (A) Extraoral image showing a facial asymmetry on the right angle of the mandible; (B) intraoral clinical image showing a soft-fluctuant swelling in the right molar-retromolar region. This image is published with the patient's consent.

Case presentation

A male patient with an age of 75 years came to the dental clinic with a swelling in the right posterior jaw region towards the angle of the mandible which was slowly growing in size over past 7 months (*Figure 1*). The patient also complained of difficulty in swallowing, occasional mild pain and pus formation. None of the past medical, surgical, personal or family history was contributing. Intraorally, there was soft fluctuant swelling in the fourth quadrant, from #46 to the ramus of the mandible. There was also evidence of lingual and buccal expansion of the swelling. There was pus oozing out on compression of the swelling. There was a previous surgical history of radicular cyst that has been enucleated three years back at the same region along with the associated tooth extraction as per the previous medical data sheet. A provisional diagnosis of residual cyst was rendered, with other differential diagnosis as odontogenic keratocyst and ameloblastoma. On fluid aspiration, a straw colored was obtained and sent for protein estimation. The value came out to be 5.2 gm/dL. The patient was sent for cone beam computed tomography (CBCT) and orthopantomogram (OPG) analysis (*Figures 2,3*).

An ill-defined, multilocular radiolucency with interrupted cortication is noted in the body and ramus of right mandible. Antero-posteriorly, it extended from the edentulous #45 region to the posterior border of ramus. Internal structure is homogeneously radiolucent. Borders are scalloped, expansion, breach of buccal and lingual cortex was observed. A diagnostic bone biopsy was obtained along with a small portion of the soft tissue material was obtained

which was sent for histopathology.

On viewing under light microscope, tumor components were seen in the form of nests and islands within the stroma (*Figure 4*). On magnification those tumor islands exhibited palisading arrangement of tall peripheral columnar cells with reversal of polarity. The center of those islands showed stellate reticulum like cells, these cells were also seen with multiple eosinophilic granules within them (*Figure 4*). The stroma showed varying levels of maturations; with few areas showed immature fibro-collagenous bundles with dystrophic calcifications (*Figure 5*). A final diagnosis of granular cell ameloblastoma was rendered.

The case was submitted for immunohistochemistry and surgical resection of the mandible was planned but unfortunately, the case was lost due to the age and financial constraints of the patient. However, it gave an immense worthy case to our case archives.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

Key findings

The unexpected emergence of a granular cell ameloblastoma subsequent to prior surgery for a radicular cyst presents a

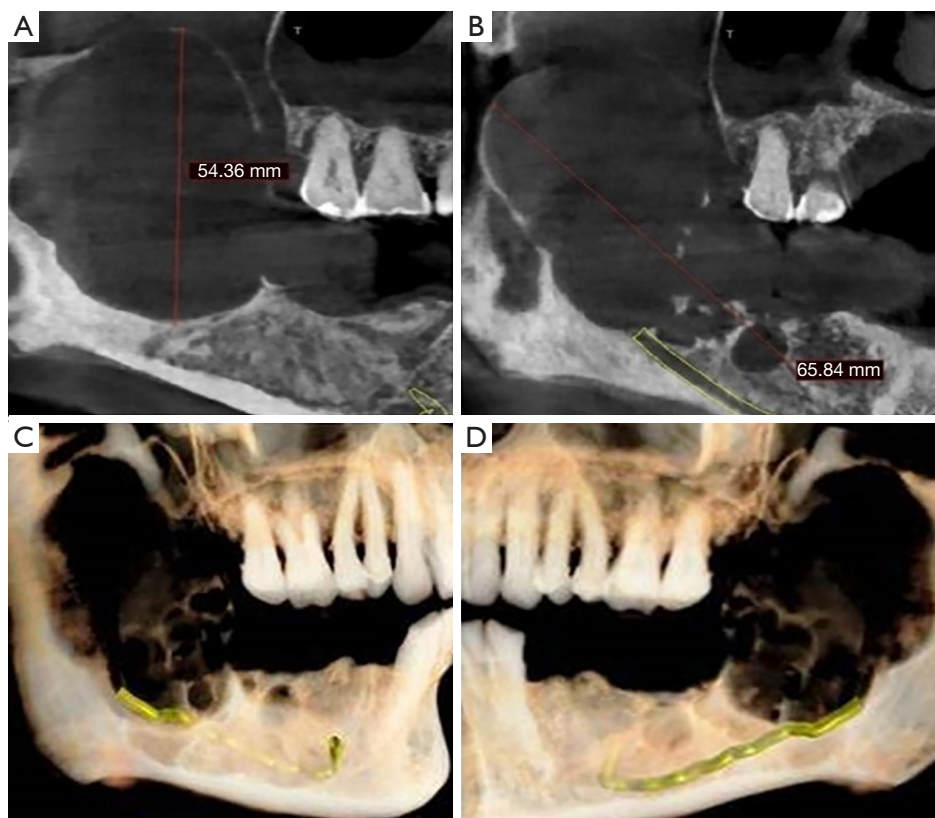


Figure 2 Radiological (digital panoramic and cone beam computed tomography images). (A,B) An ill-defined, multilocular radiolucency with interrupted cortication is seen in the body and ramus of right mandible, involving alveolar crest, ramus, sigmoid notch of the mandible and inferior border of the mandible. Breach of cortical outline of inferior alveolar nerve canal noted in posterior region. The anterior-posterior and mesiodistal extension of the lesion is measured. (C,D) The volume rendering image of CBCT showing the extension of the lesion. CBCT, cone beam computed tomography.



Figure 3 Cropped digital panoramic image showing the proximity of the lesion with the inferior alveolar nerve.

fascinating discovery. Granular cell ameloblastoma, known for its rarity, is an intriguing pathological condition. Its occurrence in an edentulous region following the treatment of a radicular cyst signifies the potentially aggressive nature of the odontogenic epithelium associated with the previously understated radicular cyst. This unexpected transition highlights the dynamic and complex nature of these lesions, shedding light on the latent aggressiveness inherent in certain odontogenic pathologies.

Strengths and limitations

This case report provides a comprehensive insight into one of the rarest variants of ameloblastoma, presenting a thorough collection of clinical, radiographic, CBCT, and histopathological images. This compilation offers a comprehensive understanding of this entity. However,

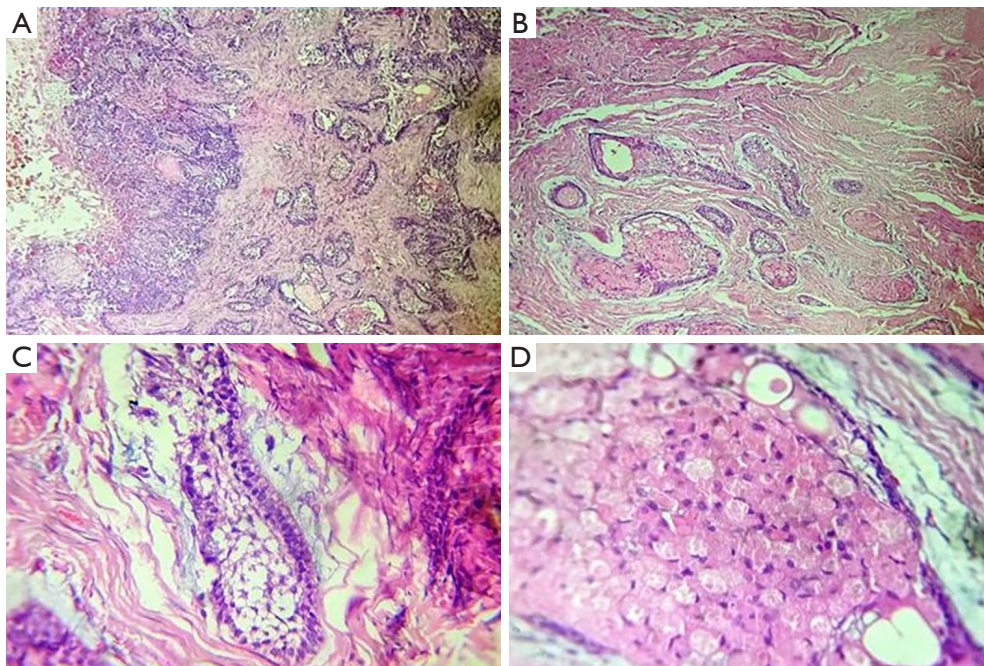


Figure 4 Histopathological features of diagnostic bone biopsy. (A,B) Tumor components in nests and islands. Mature fibrous stromal component (hematoxylin and eosin staining, $\times 4$); (C) ameloblastic islands showing palisading arrangement of tall columnar cells with central stellate cells (hematoxylin and eosin staining, $\times 40$); (D) the central stellate cells showing granular changes, numerous eosinophilic granules can be seen the cell cytoplasm (hematoxylin and eosin staining, $\times 40$).

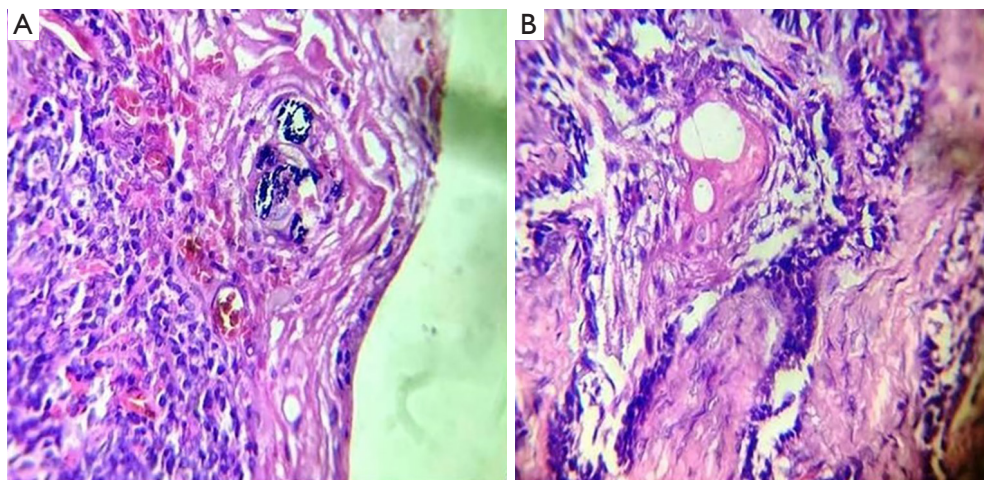


Figure 5 Histopathological images showing stromal changes. (A) Immature stroma showing dystrophic calcifications (hematoxylin and eosin staining, $\times 10$); (B) acanthomatous changes or squamous metaplasia in the cells within the ameloblastic islands (hematoxylin and eosin staining, $\times 40$).

our ability to delve deeper into its biological nature was hindered as further diagnostic investigations such as immunohistochemistry and genetic marker analysis couldn't be conducted due to the patient's absence during follow-

up, attributed to age-related and financial constraints. This incomplete aspect of our investigation leaves a gap in our understanding of the lesion's complete biological profile.

Radicular cysts, being a subset of odontogenic

lesions, often remain underexplored. Dentists may occasionally overlook sending such periapical lesions for histopathological examination. Nonetheless, the emergence of a solid ameloblastoma originating from a radicular cyst highlights the imperative need to redirect attention toward comprehending the biology of various underexplored odontogenic lesions. This case emphasizes the significance of further research and analysis to unravel the intricacies associated with these pathologies.

Comparison with similar researches

Granular cell ameloblastoma is rare type of ameloblastoma with specific histopathology and immunohistochemistry. The biological characteristics vary seldom with respect to other forms of ameloblastoma in microscopic diagnosis. However, this subtype is very aggressive and has a greater recurrence potential of 33.3% compared to other subtypes such as follicular, plexiform, and acanthomatous ameloblastoma. Alike all other ameloblastoma, the prognosis is solely based on treatment protocol whether it is unicystic or multicystic (3). Treatment done by enucleation or curettage has higher degree of recurrence therefore radical surgical procedures have a good prognosis. Rarely, granular cell ameloblastoma develop malignant potential or undergo metastasis (8-10). The creation of customized prostheses to rehabilitate excision parts (11-15).

The development of periapical radicular cyst varies from 7–54% of all periapical radiolucent lesions. Maximum of the radicular cysts occur in third to six decades of life, with male predilection and in anterior maxilla followed by the posterior maxilla, posterior mandible and then the anterior mandible. The other types of radicular cyst are lateral radicular cyst and residual radicular cyst (4). The causes of ameloblastoma (mainly unicystic) may be due to neoplastic transformation of non-neoplastic lining of the epithelium of odontogenic cysts such as radicular cyst, dentigerous cyst, and odontogenic keratocyst. A proper diagnosis and differentiation must be done to distinguish between two cases; primarily, a true ameloblastomatous cystic lining developing from a radicular cyst, secondarily chronic inflammation seen in radicular cyst/dentigerous cyst helping in development of ameloblastomatous-like epithelial lining (7,16-18).

Explanations of findings

Granular cell changes in classic cases of ameloblastoma may be found but its finding from a cystic ameloblastoma is very

rare or infrequent. Many authors tried to understand the real reason behind the granularity of the lesion. It may be due to metabolic phenomenon or as a result of degeneration. The later concept is more accepted due to the presence of death signaling molecules and its increase in number in granular cells (3). The granular cells found here are found in transitional or mature stage of ameloblastoma. The process starts from normal stellate reticulum like cells to granule production and therefore subsequent degeneration and cystic area formation (19,20). The granular cells have nuclei which are small and pyknotic and much cytoplasm. They are filled with eosinophilic granules having coarse nature suggesting apoptosis. There are various theories regarding the nature of the granularity. Their origin is epithelial and ultrastructurally and histochemically (21), they are actually lysosomes. The aggregation of lysosomes within the cytoplasm is due to altered function of lysosomal enzyme or may be caused by lysosomal-associated protein which are activating the enzyme, targeting the enzyme, or lysosomal biogenesis (19,22-25). Few immunohistochemical markers also has been studied to explore about the pathogenesis of this tumor. Expression of B-cell leukemia/lymphoma 2 protein (Bcl-2), cluster of differentiation (CD-68), and β -catenin also supports various mechanisms involved in pathogenesis. The immunohistochemical results in studies also highlights Bcl-2 negativity in granular cells suggesting apoptosis, CD-68 positivity in granular cells indicating presence of aggregates of lysosomes and β -catenin positivity for cytoplasm in granular cells showing altered pathway for cell signaling. Mouse double minute 2 (MDM2) protein was estimated for radicular cyst cases with ameloblastomatous-like change and also in cases of cystic ameloblastoma arising from radicular cysts (26-28). There are few existing reports where radicular cyst transforming into ameloblastoma are highlighted in *Table 1*.

Implications and actions needed

Diagnosis of innocuous lesion warrant formulation of differential diagnosis of even rare conditions. Careful diagnostic workup is key to the correct diagnosis and eventually treatment planing. Hence, oral diagnostic team should investigate and rule out every possible differential diagnosis.

Conclusions

Granular cell ameloblastoma is a very aggressive lesion and its development from a radicular cyst is most unique. It has

Table 1 Cases of radicular cyst transforming into ameloblastoma from published case report articles (7,29-31)

Author	Age (years) and gender	Area of occurrence and radiographic findings	Type of ameloblastoma	Treatment
Omoriegie FO <i>et al.</i> , 2015, (7)	21–40 (F > M)	Posterior mandible	Few unicystic; majority multicystic	Surgical excision
Siar CH <i>et al.</i> , 2010, (29)	38/F	Mandibular premolar-molar region, well-defined unilocular radiolucency (scalloped, sclerotic margins)	Follicular and mural	Surgical excision
Mahajan AD <i>et al.</i> , 2014, (30)	68/M	Mandibular alveolar ridge, oval radiolucency surrounded by well-defined radiopaque margin in lower part	Unicystic and follicular	In toto enucleation
Fedhila M <i>et al.</i> , 2022, (31)	23/M	Mandible, well-circumscribed unilocular radiolucency with a sclerotic border	Unicystic and mural	Surgical resection and enucleation

F, female; M, male.

higher propensity for recurrence if not treated properly and therefore any type of lesion must be diagnosed properly and thoroughly examined. After its detection, the treatment protocol of granular cell ameloblastoma must be decided appropriately since it may also develop metastasis.

Acknowledgments

We sincerely thank Dr. Amartya Dutta, Dental Surgeon for the case record maintained and Aniruddha Banerjee, Histotechnician for the histopathology slide preparation.

Funding: None.

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at <https://jphe.amegroups.com/article/view/10.21037/jphe-23-114/rc>

Peer Review File: Available at <https://jphe.amegroups.com/article/view/10.21037/jphe-23-114/prf>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://jphe.amegroups.com/article/view/10.21037/jphe-23-114/coif>). G.M. serves as an unpaid Editorial Board member of *Journal of Public Health and Emergency* from September 2023 to August 2025. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are

appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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doi: 10.21037/jphe-23-114

Cite this article as: Banerjee A, Wati SM, Das M, Srivastava KC, Shrivastava D, Ronsivalle V, Franco R, Cicciù M, Minervini G. Aggressive granular cell ameloblastoma arising from radicular cyst: a case report of an unusual variant and a public health concern. *J Public Health Emerg* 2024;8:10.