Scientific Foundation SPIROSKI, Skopje, Republic of North Macedonia
Open Access Macedonian Journal of Medical Sciences. 2025 Jun 15; 13(2):122-127.
https://doi.org/10.3889/oamjms.2025.12115
eISSN: 1857-9655
Category: *C – Case Reports*
Section: *Case Report in Dentistry*

Unicystic Ameloblastoma: Case Report with Insights into Molecular and Immunological Pathogenesis

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Citation: Bizevski D, Popovski V, Bajramov E, Hristomanova-Mitkovska S. Unicystic Ameloblastoma: Case Report with Insights into Molecular and Immunological Pathogenesis. Open Access Maced J Med Sci. 2025 Jun 15; 13(2):122-127. https://doi.org/10.3889/oamjms.2025.12115
Keywords: Unicystic ameloblastoma; odontogenic tumor; BRAF V600E; MAPK signaling; Wnt signaling; TNF-α; immunopathogenesis; surgical management
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Received: 27-Feb-2025
Revised: 01-May-2025
Accepted: 10-Jun-2025

Funding: This research did not receive any financial support
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Unicystic ameloblastoma is a benign yet locally aggressive odontogenic tumor, predominantly affecting the mandible in young adults. Its pathogenesis involves dysregulation of odontogenic signaling pathways, including MAPK, Wnt/β-catenin, and Sonic Hedgehog, as well as molecular alterations affecting proliferation and extracellular matrix remodeling. Activating BRAF V600E mutations and cytokine-mediated mechanisms, such as osteoclast activation, contribute to tumor growth and local invasiveness. We aimed to present a case of unicystic ameloblastoma and discuss its clinical, radiographic, and histopathological features, with emphasis on molecular and immunological mechanisms relevant to management.

CASE REPORT: A 40-year-old female presented with a persistent, firm swelling in the anterior mandible. CBCT revealed a unilocular radiolucent lesion involving teeth 32 and 33. Preoperative endodontic therapy was performed, followed by surgical enucleation under local anesthesia. Histopathology confirmed a unicystic plexiform ameloblastoma. Postoperative healing was uneventful, and one-year follow-up imaging showed no recurrence.

CONCLUSION: Local invasiveness and recurrence are driven by molecular and immunological mechanisms, including BRAF V600E mutations, MAPK/Wnt signaling dysregulation, and TNF-α–mediated stromal interactions. Complete surgical removal with careful follow-up remains critical for favorable outcomes.

Introduction

Mandibular swellings are often caused by benign lesions of odontogenic or non-odontogenic origin, including ameloblastoma, radicular and dentigerous cysts, keratocystic odontogenic tumors, central giant cell granulomas, fibro-osseous lesions, and osteomas [1]. Ameloblastoma is a benign odontogenic tumor arising from epithelial components involved in tooth development, such as the enamel organ, dental lamina remnants, odontogenic cyst linings, or possibly basal oral mucosal cells [2].

A comprehensive 2022 review found that 89% of ameloblastomas (999 cases) occur in the mandible, compared to 11% (121 cases) in the maxilla, making mandibular cases eight times more common [3].

Ameloblastoma is the second most common odontogenic tumor worldwide, with an incidence of about 0.5 cases per million annually [4]. It is more prevalent in Africa, China, and among African Americans, and shows a slight male predominance, with a male-to-female ratio of 1.2:1 [3], [5]. Most cases occur between ages 30 and 60, with average diagnosis ages of 42.3 in Europe and 30.4 in Africa [6]. Although pediatric cases are uncommon (10–15%), they may reach up to 25% in Africa and Asia [7].

The 2017 WHO classification identifies four types of ameloblastoma: conventional (solid/multicystic), unicystic, peripheral, and metastasizing [8].

Conventional ameloblastoma, the most common subtype (approximately 91%), is typically slow-growing and benign. Histologically, it mainly shows follicular patterns with epithelial islands or plexiform patterns with interconnected strands, often mixed. Less common variants include cystic, granular, acanthomatous, spindle cell, basal cell, and clear cell

types [9], [10].

Peripheral ameloblastomas are a rare subtype characterized by a benign course with minimal bone involvement. They primarily occur in the mandible, especially in the gingival tissue. Their origin is believed to be from odontogenic remnants of the vestibular lamina, pluripotent cells in the basal mucosal epithelium, or minor salivary gland cells, supporting the view that peripheral ameloblastomas are true neoplasms rather than developmental hamartomas [11].

Unicystic ameloblastoma (UA), the second most common subtype (5–15% of cases), primarily affects younger patients (average age 26.1) and typically appears as an asymptomatic swelling in the posterior mandible [12]. Often associated with unerupted teeth, it closely resembles dentigerous cysts and can sometimes be difficult to distinguish from them [13].

Unicystic ameloblastoma (UA) mimics an odontogenic cyst but is distinguished histologically by the presence of ameloblastomatous epithelium, which may exhibit growth either into the lumen or the cyst wall [14]. UA is classified into three histological variants: luminal, with tumor cells limited to the cyst lining; intraluminal (plexiform), showing tumor projections into the cyst lumen; and mural, where tumor islands infiltrate the cyst wall. Often, multiple variants coexist within a single lesion [9].

Etiology and Pathogenesis

Although classified as benign, ameloblastomas exhibit locally aggressive behavior and carry a high risk of recurrence if not completely exercising. In rare cases, they may undergo malignant transformation with distant metastases or participate in tumor-to-tumor metastasis [15], [16].

The mechanisms underlying their invasiveness remain unclear, though studies suggest it involves degradation of the basement membrane and extracellular matrix, enabling tumor cell proliferation. This process may be driven by the secretion of matrix metalloproteinases and other bioactive molecules that stimulate mitogen release and further promote tumor growth [17].

The exact etiology of ameloblastoma remains unclear, though early theories have linked it to trauma, inflammation, nutritional deficiencies, and dental caries [10]. Odontogenic tumors are believed to arise from residual epithelial cells that migrate during tooth development, especially near the cervical loop of the enamel organ. Similarly, ameloblastomas are thought to originate from these enamel organ remnants, other odontogenic epithelial cells, or the lining of odontogenic cysts [18]. This theory is supported by similar protein markers—cytokeratin and vimentin—found in both developing tooth tissues and ameloblastoma cells [19]. Several theories have been proposed to explain ameloblastoma development. One theory suggests that pre-ameloblasts fail to mature during the bell stage due to absence of the stratum intermedium, which produces alkaline phosphatase necessary for nutrient transfer, as demonstrated by impaired enamel formation in Msx-2 deficient mice [20]. Another theory proposes that pre-ameloblasts continue to proliferate without differentiating into functional ameloblasts, failing to produce enamel proteins or matrix during this stage [21]. While these early hypotheses provided valuable insights, from 2015 onward, growing evidence has pointed to genetic and molecular abnormalities in various signaling pathways as key drivers of ameloblastoma development, aggressiveness, and metastatic potential. At the molecular level, ameloblastoma is characterized by dysregulation of genes essential for odontogenesis and epithelial–mesenchymal signaling. Gene expression analyses have shown upregulation of genes associated with cellular proliferation and matrix remodeling (*FOS, TNFRSF1A, MMP-12, MMP-13*) and downregulation of key developmental pathways, including *SHH, PTCH, BMP2*, and *TGFB1*, when compared with normal odontogenic tissue [22]. These alterations contribute to abnormal odontogenic epithelial behavior and tumor development.

Recent molecular studies have identified overexpression of *WNT5A* and *WNT1*, implicating aberrant WNT signaling in the development of ameloblastoma [23]. Evidence from tumor samples, cell lines, and transgenic models first highlighted the role of MAPK pathway dysregulation in ameloblastoma development. Activating mutations in BRAF, a key MAPK/ERK regulator, were identified in over 63% of ameloblastomas, with the V600E substitution accounting for more than 90% of these cases [24], [25].

Subsequent studies confirmed these findings and expanded them, reporting additional alterations in upstream MAPK regulators, including RAS and FGFR2, further supporting the central role of this pathway [4], [26]. Mutations in non-MAPK signaling components, particularly SMO of the Sonic Hedgehog pathway, were also described later, highlighting alternative molecular mechanisms contributing to ameloblastoma pathogenesis [27]. Collectively, these studies underscore distinct molecular abnormalities driving ameloblastoma.

Building on the current understanding of ameloblastoma pathogenesis, including dysregulation of odontogenic and MAPK/WNT signaling pathways, clinical presentations remain variable and often require careful assessment.

This report aims to present a case of unicystic ameloblastoma and to discuss its clinical, radiographic, and histopathological features, along with current understanding of its molecular and immunological pathogenesis and considerations for optimal management.

Case report

Patient History

A 40-year-old female was referred to our clinic for evaluation of a persistent swelling in the lower jaw, specifically in the vestibular region of teeth 32 and 33. The swelling had been present for an extended period, showing no signs of regression, and was associated with constant pain and a sensation of pressure. The patient reported no significant medical history or other relevant systemic conditions.

Clinical Findings

Extraoral examination revealed a subtle asymmetry in the lower third of the face at the mental region, corresponding to a localized swelling (Figure 1).

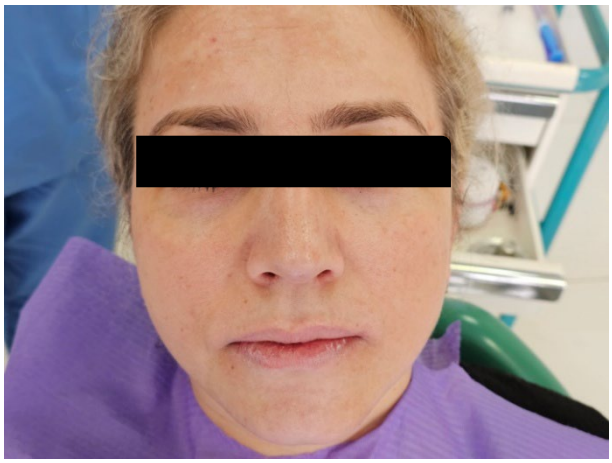

Figure 1: Extraoral presentation of the swelling in the mental region

Intraorally, the dentition had been conservatively treated and prosthetically restored. The vestibular region of the anterior mandible, particularly around teeth 31, 32, and 33, demonstrated a firm, non-fluctuant soft tissue swelling (Figure 2). The gingiva and adjacent soft tissues appeared healthy, with no signs of infection.

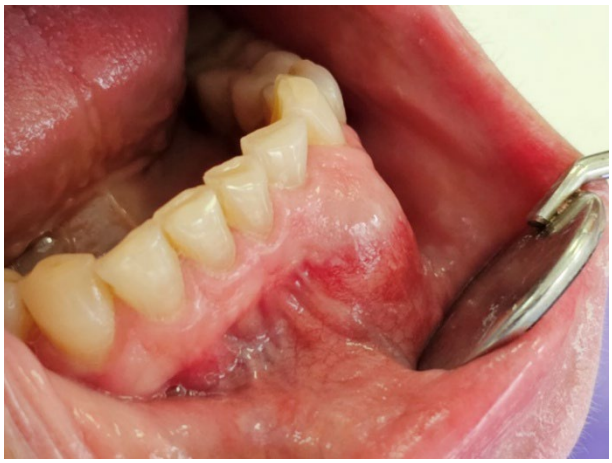

Figure 2: Intraoral view showing the swelling in the vestibular region of the anterior mandible

Radiographic Findings

Panoramic radiography revealed a well-defined, pear-shaped radiolucent lesion in the region of teeth 32 and 33, associated with slight tilting of the adjacent teeth (tooth 32 tilted distally, tooth 33 tilted mesially) (Figure 3a). For a more detailed evaluation, cone-beam computed tomography (CBCT) was performed, demonstrating a radiolucent area that had completely eroded the buccal cortical plate and extended into the surrounding soft tissues (Figures 3b and 3c). The lesion measured 12.8 mm mesiodistally, 12.4 mm buccolingually, and 18.7 mm craniocaudally (Figures 3b and 3d). The lingual cortical plate of the mandible was partially preserved along its full dimension, with fenestration noted in the middle third. The lesion was in close proximity to the roots of teeth 32 and 33, suggesting a possible odontogenic origin, potentially of an infectious nature.

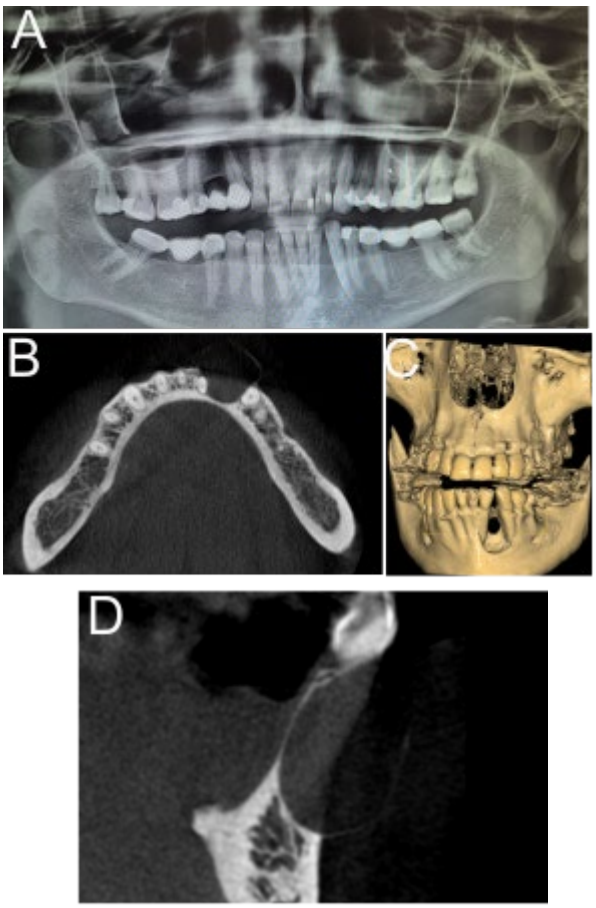

Figure 3: Radiographic findings. (A) Panoramic radiograph showing a well-defined, pear-shaped radiolucent lesion in the region of teeth 32 and 33, with slight tilting of the adjacent teeth; (B) Transversal CBCT measurements of the lesion, indicating mesiodistal, buccolingual; (C) 3D skull CBCT view showing the lesion's radiolucent area and its relationship to adjacent soft tissues; (D) Sagittal CBCT view demonstrating complete erosion of the buccal cortical plate and extension into the surrounding soft tissues and craniocaudal dimensions

Additional Investigations

Preoperative pulp vitality testing of teeth 32 and 33 revealed reduced sensitivity to electrical stimuli.

Aspiration biopsy yielded a clear, yellowish fluid.

Therapy

The unclear clinical and radiographic presentation of the lesion indicated the need for preoperative endodontic treatment of teeth 32 and 33. Due to the uncertain ethology and the lesion's extent, surgical intervention was considered the only justified approach. Under local anaesthesia, a mucoperiosteal flap was elevated following a Nowak-Peter incision. Macroscopically, the cystic lesion extended into the surrounding buccal and lingual soft tissues, with complete destruction of the buccal cortical plate and fenestration of the lingual cortical plate (Figure 4a). The lesion was carefully dissected and enucleated entirely up to healthy bone and soft tissue margins. Apicoectomy was performed on teeth 32 and 33, and the integrity of the canal fillings was verified macroscopically (Figure 4b).

The surgical field and flap were thoroughly irrigated with a tetracycline antibiotic solution. A haemostatic agent (CollaFleece) was placed in the bony defect to promote bone healing (Figure 4c). Postoperative hemostasis was achieved after flap closure (Figure 4d), and the sutured flap is shown in Figure 4e.

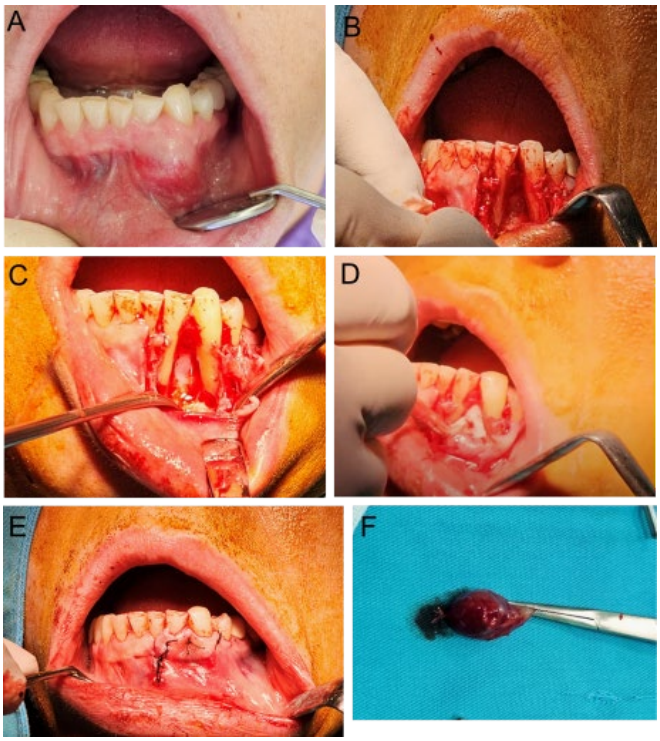

Figure 4: Surgical procedure and postoperative findings. (A) Macroscopic view of the cystic lesion extending into buccal and lingual soft tissues, with destruction of the buccal cortical plate and fenestration of the lingual plate; (B) Apicoectomy of teeth 32 and 33 with verification of canal fillings; (C) Placement of hemostatic agent (CollaFleece) in the bony defect; (D) Postoperative hemostasis after flap closure; (E) Sutured mucoperiosteal flap demonstrating proper closure; (F) Excised tissue specimen showing cystic formation with wall thickness of 0.2–0.4 cm

The patient was prescribed antibiotics (Amoxiclav 1000 mg, twice daily for 7 days) and anti-edema therapy. The excised tissue was submitted for histopathological analysis, consisting of irregular soft-tissue fragments measuring 2 × 1 cm and 1 × 0.7 cm, containing a cystic formation with a wall thickness of 0.2–0.4 cm (Figure 4f).

Results

Histopathological analysis of the excised tissue revealed a cystic formation containing plexiform strands and nests of odontogenic epithelial cells with classic peripheral palisading, as well as islands of desmoplastic compression of odontogenic cells, with areas of acanthomatous and basaloid metaplasia. The lesion was well-circumscribed by a connective tissue capsule, consistent with a unicystic ameloblastoma of the plexiform type.

Periapical lesions are common in the oral cavity and frequently have an odontogenic origin [28]. Empirical diagnosis and management of such lesions, particularly when the clinical presentation deviates from the typical pattern, can often lead to inappropriate treatment over prolonged periods. Modern diagnostic protocols, including radiographic analysis using contemporary imaging techniques and preoperative biopsy, allow for accurate differentiation and are essential before initiating surgical intervention. Since initial patient contact often occurs in general dental practice, timely referral to an oral or maxillofacial surgeon is critical for successful management and predictable long-term outcomes.

Discussion

Ameloblastoma is a benign odontogenic neoplasm with locally aggressive behavior, extensive bone destruction, and a notable tendency for recurrence despite its benign histological appearance [25], [29]. This paradoxical behavior reflects the interplay between intrinsic molecular alterations within tumor cells and immunologically mediated mechanisms in the surrounding bone microenvironment.

At the molecular level, ameloblastoma is characterized by dysregulation of signaling pathways essential for odontogenesis and epithelial–mesenchymal interactions. Altered expression of genes involved in cellular proliferation, differentiation, and extracellular matrix remodeling has been consistently reported, including components of the mitogen-activated protein kinase (MAPK), Sonic Hedgehog (SHH), and Wnt/β-catenin pathways [24], [30], [31]. In particular, cytokine-mediated activation of the mitogen-activated protein kinase (MAPK) pathway—including tumor necrosis factor-α (TNF-α)–dependent signaling—has been implicated in promoting tumor cell survival, proliferation, and

extracellular matrix remodeling [31]. Among these, activating mutations in the MAPK pathway play a dominant role. The BRAF V600E mutation has been identified in a majority of ameloblastomas and leads to constitutive activation of downstream signaling, promoting tumor cell survival and proliferation [6], [7]. Additional alterations in upstream regulators such as RAS and FGFR2 further reinforce the central role of MAPK signaling in tumor pathogenesis [32], [33].

Local invasiveness is further facilitated by increased expression of matrix metalloproteinases (MMPs), particularly MMP-2, MMP-7, MMP-9, and MMP-13, which contribute to extracellular matrix degradation and bone infiltration [30], [34], [35]. Concomitantly, dysregulation of apoptosis-related pathways has been demonstrated, including overexpression of anti-apoptotic proteins such as heat shock protein-70 (HSP-70) and altered p53 activity, enabling tumor persistence and resistance to cell death [36], [37], [38].

In addition to intrinsic molecular abnormalities, immunological mechanisms play a critical role in ameloblastoma progression, particularly in the context of bone invasion. Tumor expansion within bone requires not only cellular invasiveness but also active osteolysis mediated by osteoclasts [39]. Osteolytic lesions associated with ameloblastoma are characterized by increased recruitment and activation of osteoclasts, which are often observed both adjacent to tumor tissue and at distant sites within the bone, suggesting the involvement of paracrine signaling mechanisms [40], [41].

The tumor–bone microenvironment in ameloblastoma is enriched with pro-inflammatory and immunomodulatory mediators, including tumor necrosis factor-α (TNF-α), interleukins IL-1β, IL-6, IL-8, IL-11, IL-17, activin A, and receptor activator of nuclear factor-κB ligand (RANKL) [31], [32], [42]. These cytokines promote osteoclastogenesis, inhibit osteoblast differentiation, and support tumor progression within the mineralized bone matrix.

Emerging evidence indicates that ameloblastoma cells actively modulate this pathway through cytokine-mediated crosstalk with stromal cells. Direct interactions between tumor cells and bone marrow stromal fibroblasts have been shown to induce expression of IL-8 and activin A, which synergize with RANKL to enhance osteoclast differentiation and function [33], [42]. IL-8 additionally exhibits chemotactic and pro-angiogenic properties, further contributing to tumor survival and local expansion within bone [43].

Taken together, the convergence of molecular dysregulation, resistance to apoptosis, cytokine-mediated osteoclastogenesis, and tumor–stromal interactions provides a comprehensive explanation for the locally invasive nature and recurrence tendency of ameloblastoma. These intertwined mechanisms highlight the importance of integrated molecular and immunological evaluation in improving diagnostic accuracy, prognostic assessment, and the development of targeted therapeutic strategies.

Literature on ameloblastoma recurrence varies with etiology, tumor type, location, and treatment modality. Conservative treatments such as simple enucleation or curettage are associated with higher recurrence rates, ranging from 55–90% within the first few postoperative years. Surgical resection with margins extending to healthy tissue is considered safer, with recurrence rates of 10–15%. Prognosis for unicystic ameloblastomas is generally more favorable than for multicystic lesions, due to compactness and surgical accessibility for complete removal [44], [45], [46].

In the present case, surgical enucleation without segmental mandibular resection was considered appropriate due to the favorable anatomical location of the tumor, the patient's relatively young age, and the feasibility of complete in toto removal. Optimal management of ameloblastoma depends on early detection and accurate differentiation from other jaw lesions. Careful postoperative clinical and radiographic monitoring is particularly important during the first year, which represents the period of highest recurrence risk.

Conclusion

Ameloblastoma is a benign odontogenic tumor that exhibits locally aggressive behavior, driven by intricate molecular alterations and immunological mechanisms. Its pathogenesis involves dysregulation of signaling pathways, resistance to apoptosis, and cytokine-mediated interactions with the bone microenvironment, which collectively contribute to local invasiveness and recurrence potential. Accurate diagnosis relies on a combination of clinical, radiographic, and histopathological assessment, while surgical management should be tailored to tumor location, size, and patient factors. Complete removal with careful follow-up, particularly during the first year postoperatively, remains essential for minimizing recurrence and ensuring optimal long-term outcomes.

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