

Locally Aggressive Case of Ameloblastoma With 15 Years Follow-Up: A Case Report

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Abstract

Ameloblastomas (AM) are the most common benign odontogenic tumors with local invasion and high recurrence rates, which generally occur in the jawbones. Although most cases occur between ages 20 and 40, AM can still occur in children at a much lower incidence. Ameloblastomas typically exhibit an aggressive nature, with the potential to infiltrate the jawbone and present as a noticeable tumor.¹ About 1% of oral tumors are found to be ameloblastoma.² This paper presents a case report of a 40-year-old female diagnosed with a giant ameloblastoma of the left lower mandible who had multiple surgeries done for local recurrences over 15 years duration.

Keywords: Ameloblastoma, recurrence, case report, radiotherapy

Introduction

Ameloblastoma is a benign tumor that occurs most frequently in the mandible bones, accounting for 1% of oral tumors. It originates from the remains of a tooth enamel organ, which is a group of epithelial cells in the developing teeth. As a slow-growing and locally invasive tumor, ameloblastoma peaks in the 3rd decade with a slight male predominance. In 2022, the 5th edition classification of the Head and Neck Tumors published by the World Health Organization (WHO, Geneva, Switzerland), five separate AM types are identified within the benign epithelial odontogenic tumors category: unicystic AM, extraosseous/peripheral AM, conventional AM, adenoid AM, and metastasizing AM.³ Since recurrence rates are significantly lower after radical treatment than with conservative forms, surgery is often the recommended treatment for ameloblastoma. Systemic treatment modalities are also used in recurring and metastasizing cases. Other forms of additional therapies are curettage, chemical and electrocautery, radiation therapy, or a combination of them.² Although histologically benign, AMs exhibit a locally invasive growth pattern and a high recurrence rate. Conservative treatment can maximize the preservation of normal tissue and reduce maxillofacial deformities, while the recurrence rate after surgery is quite high.⁴ The main objective of radical treatment is the complete removal of the tumor and the marginal tissue at risk for infiltration of tumor cells to minimize recurrence.^{5,6} However, this approach leads to severe maxillofacial deformity and results in compromised stomatognathic function, which causes impaired quality of life as well as psychological distress. Therefore, oral and maxillofacial surgeons are faced with a dilemma between conservative treatment and radical treatment when dealing with patients with a giant AM.⁷

In the advanced stages, patients often suffer from a range of severe complications.

We present a challenging case of a left mandibular AM with multiple surgeries. The patient's tumor grew aggressively after several surgeries with locoregional recurrences that necessitated external beam radiation application and anti-BRAF targeted therapy administration. The patient had completed 15 years of follow-up with three-stage reconstruction surgery planned to correct the surgical site deformity. Small mandible lesions may only require a conventional radiograph. On the other hand, lesions in the maxilla or extensive lesions need CT and MRI scans to determine the scope of the lesions.

Case Report

Our patient is a 40-year-old Asian lady, she is the mother of six children, with no significant past medical history. She consulted a faciomaxillary surgeon in Feb 2007 complaining of painful left lower jaw swelling. Radiological imaging showed a mass below the left wisdom tooth that was reported as a wisdom tooth cyst. The lesion was excised and histopathological examination (HPE) showed ameloblastoma of mixed follicular and plexiform pattern (Figure 1). The patient was reassured about the benign nature of the tumor and kept on follow-up until Apr 2009 when she had a local disease recurrence (Figure 2). Excised again, HPE was consistent with recurrent ameloblastoma.

Six months later in Nov 2009, the lesion locally recurred and completely re-excised but HPE reported the tumor to be a basal cell adenoma.

In 2011, the disease recurred for the fourth time and the faciomaxillary surgeon removed part of the left mandible with negative margins. Several months following this operation patient consulted a plastic surgeon in Iran who put a graft at the site of previous disfiguring surgeries but the graft was removed 6 months later because of severe intolerable pain.

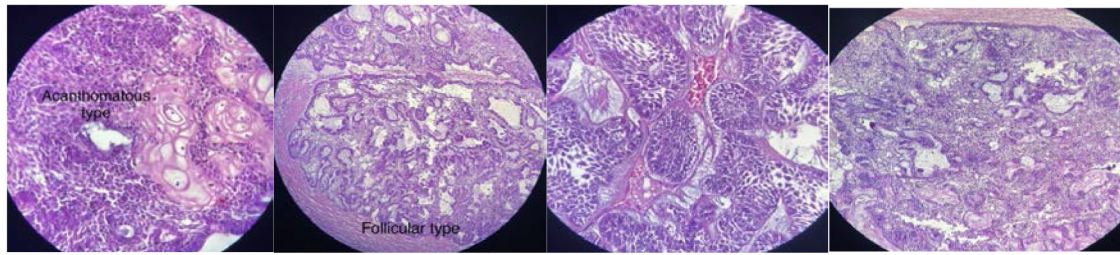


Fig. 1 Histopathological examination of the samples revealing both acanthomatous and follicular patterns of the recurred Ameloblastoma tumor.



Fig. 2 Clinical extraoral image shows large swelling at left lower jaw causing facial asymmetry with first recurrence.

Follow-up ultrasonography (U/S) of the neck in Jan 2013 showed a left thyroid lobe nodule; hence left thyroid lobectomy was done because of diagnostic uncertainty but the HPE was consistent with nodular colloid goiter with no evidence of malignancy. In Jul 2013, the disease recurred locally and resected for the fifth time and HPE was in keeping with completely excised pleomorphic adenoma.

One year later in 2014, she returned with another mass at the site of the previous operation. The mass was resected surgically with free tumor margins and HPE revealed a 4 cm ameloblastoma of a follicular and plexiform pattern at the pterygomaxillary and left inferotemporal area. Subsequently, 20 fractions of adjuvant radiotherapy (RT) were given to the left mandibular area.

In Nov 2015, the patient started to complain of pain in her left lower jaw and U/S of the neck showed a 16 mm mass in the posterior portion of the left submandibular gland. Fine needle aspiration cytology (FNA/C) from this nodule revealed the same ameloblastoma pathology. The faciomaxillary surgeon resected the mass with submandibular gland removal and the pathology was consistent with a borderline recurrent ameloblastoma of the same histologic type.

In Nov 2016, the patient developed 4 local masses 2–3 cm in size at the left cervical and submandibular areas. All the excised lesions revealed recurrent AM; follicular and acanthotic subtypes (Figure 1), in addition to a single reactive submandibular lymph node.

In May 2017, a scheduled follow-up CT scan showed a solitary lesion at the left submandibular area with multiple cystic changes and enhancement on intravenous contrast. Biopsy was consistent with a recurrent follicular ameloblastoma. MRI of the head and neck showed multiple enhanced masses, hypointense on T1WI, hyperintense on T2WI highlighted post-STIR T2WI, at the left submandibular area and few deeply seated lesions within the left sublingual area (at least 5 lesions measuring 17.5, 12, 15, 10.5 & 8 mm). All lesions were excised and all showed recurrent ameloblastoma.

In Jul 2018, the patient felt a lump anterior to the left auricle. U/S showed a relatively well-defined hypoechoic lesion of 24*14 mm at the left parotid gland in addition to a complex cystic lesion of 34*17 mm at the upper outer canthus of the left eye. She had surgical resection of these pterygomaxillary and infratemporal masses. HPE revealed a 4 cm mass with the same pathology (recurrent ameloblastoma). All excision margins were negative for the disease. The surgery was followed by RT for the second time (3000 cGy over 10 fractions).

In Apr 2019, a follow-up MRI showed 3 enhancing bony lesions involving; the left zygomatic bone, left the zygomatic process of the frontal bone, measured (4*3*2 cm), encroaching left orbit, and causing left exophthalmos, two other enhancing lesions seen involving left temporal bone measuring (1.5 & 1.7 cm) with abnormally enhanced thickened sphenoid bone bilaterally with signs of bilateral cavernous sinus invasions.

On 3 May 2019, a repeat MRI (Navigation Protocol) plus FDG-PET CT scan in India showed an expansile lobulated cystic-solid heterogeneous intensity mass lesion on the roof and lateral wall of the left orbit, solid component showed heterogeneous contrast enhancement. It measured 22.7*20.7*40.4 mm (TR, AP, CC dimensions), and it bulges into the extraconal component abutting the left superior and lateral recti muscles. Similar enhancing nodular lesions are seen in the greater wings of the sphenoid, left zygoma, left frontal, left ramus of the mandible, and bilateral petroclival areas reaching bilateral cavernous sinuses. All the lesions were inhomogeneously FDG avid by PET component that also showed a right thyroid lobe nodule, multiple subcentrimetric cervical lymph nodes, and an enlarged liver (18.8 cm).

On 16 May 2019, she had an excision of a left orbital tumor in India (CK Birla Hospital for Women).

In Jan 2020, she received a third course of RT (4005 cGy over 15 fractions to petroclival mass + variables + margins).

In Apr 2021, an MRI showed disease progression with 3 lesions near the zygomatic bone in addition to surgical bed mass (Figure 4). These lesions were ablated by the Stereotactic Radiosurgery (SRS) in Turkey.

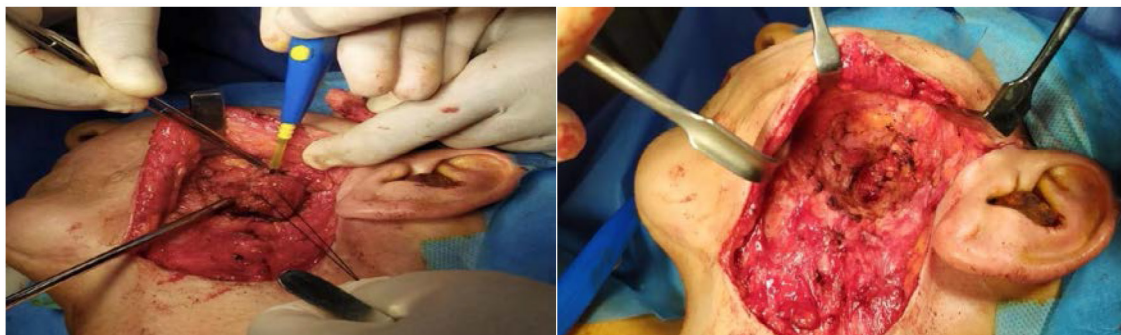


Fig. 3

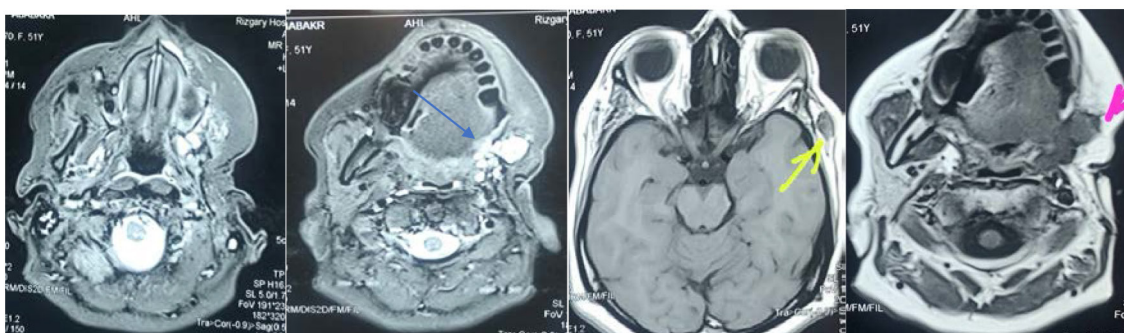


Fig. 4 An MRI shows 3 zygomatic lesions plus surgical bed mass.



Fig. 5 Shows necrosis/fistula at the left Oro-Nasal part of the hard palate.

The later specimen tested positive for BRAF V600E mutation therefore she commenced on Vemurafenib oral tablets 240 mg twice a day starting in Oct 2021; she had continuous Grade-III fatigue despite a 50% dose reduction. In Dec 2021, she developed a hemorrhage at the site of surgery with resulting hard palate necrosis and fistula formation (Figure 5), Vemurafenib was stopped and the faciomaxillary surgeon was consulted.

She underwent a free fibula flap for hemi-mandibulectomy defect reconstruction and free anterolateral (ALT) flap transfer for external skin on 10 Apr 2023.

She underwent flap thinning and free functional Gracilis muscle flap for facial re-animation and face lift [superficial musculoaponeurotic system (SMAS) plication] for the right

side done on 30 Oct 2023. The patient had dark-colored blood in the flap, so she was taken for re-exploration and Gracilis free flap exploration and salvage flow through anterolateral (ALT) free flap done on 01 Nov 2023. Our patient is alive with a better look and planning for the third stage of reconstruction in Feb 2024.

Discussion

Ameloblastomas, known for their benign, slow-growing but locally aggressive nature, often demand surgical intervention. “Ameloblastoma” originates from ‘amel’ which stands for enamel and ‘blastos’, which denotes germ. Ameloblasts, cells originating from oral ectodermal cells are responsible for the production of enamel.¹ Ameloblastomas tend to invade bone, as well as soft tissues. This odontogenic tumor generally peaks in the third decade and the mean age was 34 years. A slight male preference (53%) was found, and the mandible appeared to be the preferred site. Although Ameloblastomas are common odontogenic tumors, they represent only 1% of head and neck cancers.⁶

Ameloblastoma is found to be the second most common odontogenic tumor after odontoma.⁸ Ameloblastoma can be of several types, including solid/multicystic, extraosseous/peripheral, desmoplastic, or unicystic. The solid/multicystic form is present in 10% of odontogenic tumors of the jaw.² The development of this solid tumor may be due to several signaling pathways such as MAPK, WNT, Akt, and FGFs.^{2,9,10} This type manifests most frequently in the posterior region of the mandible. The posterior mandible is a region frequently affected by ameloblastoma. Histologically, it is difficult to distinguish benign ameloblastoma from malignant cases, as they

appear identical. The only differentiation visible between benign and malignant cases is the degree of invasion or metastasis.¹¹ Lungs are the most common site for metastasis.¹² Secondary cases of ameloblastoma from primary squamous cell carcinoma of the lung display signs of malignancy on histology but not the classic features of ameloblastoma including polarization, peripheral palisading, and stellate cells.¹ There are six histological types of solid ameloblastoma: follicular, plexiform, acanthomatous, basal cell, granular, and DA. Mixtures of these types can be observed, such as in this case where there are both follicular and plexiform patterns present. Bone erosion is a common feature of this solid type, and it was also observed in this case in which the patient's left mandible had to be removed. The follicular types tend to recur the most. Due to its high recurrence rate, solid/ multicystic ameloblastomas almost always require surgical resection.²

Peripheral ameloblastoma involves the gingiva or alveolar mucosa with no bone involvement. Desmoplastic ameloblastoma is distinguished by desmoplasia and atypical histomorphology. Unicystic ameloblastoma is a rare form commonly seen in younger age groups. Ameloblastoma may be seen as unilocular (no septum present) or multilocular on a conventional radiograph. In multilocular cases, ameloblastoma may have the following appearances: honeycomb or soap bubble appearance or tennis racket pattern. Other common features that may be more specific to ameloblastomas include buccal and lingual cortical plate expansion.²

The typical presentation of ameloblastoma is a painless mass, therefore it is often overlooked.² If pain is present, it is a result of bleeding in the tumor or around the tumor. Complications of ameloblastoma include local invasion of surrounding tissues, distant metastasis, facial deformity, airway occlusion, and pain.¹³ History and physical examination aid in the diagnosis of ameloblastoma, alongside imaging such as CT scan. Ameloblastoma is visualized as a radiolucent lesion on a CT scan. There is also multilocular (soap-bubble appearance). There may also be bony expansion, tooth root resorption, and unerupted teeth.¹ Ameloblastoma is confirmed only with biopsy which can aid in differentiating it from other diagnoses such as ossifying fibroma, giant cell tumor, osteomyelitis, cystic fibrous dysplasia, myeloma, and sarcoma.^{9,14,15} According to the WHO classification, malignant ameloblastoma can be divided into two types; metastasizing AM and ameloblastic carcinoma. Metastasizing ameloblastoma is the same as benign ameloblastoma in histology but has metastasis. As for

ameloblastic carcinoma, it has malignant features histologically and is also divided into primary and secondary forms.¹ For primary ameloblastic carcinoma, the prognosis is better than secondary cases of carcinoma. Yang et al. developed a system for staging ameloblastomas according to clinicopathological signs; in stage 1, the tumor diameter is ≤ 6 cm; in stage 2, the tumor is > 6 cm or there is tumor invasion into the maxilla or floor of the orbits; and lastly, stage 3, in which the tumor has invaded the base of the skull or there is regional lymph node metastasis. The earlier the recurrence of the tumor, the latter is expected the stage of the tumor.¹⁵

Treatment planning involves surgical resection with safety margins that may be followed by chemoradiotherapy. Due to their benign nature, they are chemo-resistant. Only case reports utilized chemotherapy for malignant ameloblastoma.^{16,17} Novel anti-BRAF targeted therapies like Vemurafenib were also used since most tumors harbor BRAF V600E mutation.^{11,18} Other treatment modalities include enucleation and curettage, cryotherapy, and marsupialization.¹² However, these treatments are only supportive as surgery is the preferred mode of treatment.¹ Surgery may lead to facial deformities, therefore conservative treatments, such as enucleation and curettage, were tried but not successful due to high recurrence rates. A three-fold increase in recurrences has been observed in conservative treatment of ameloblastoma as compared to radical treatment.^{19,20} Treatment of ameloblastoma is dependent on the size, location, and histology. For the mandible, if the lesion is < 1 cm on radiographic imaging, then curettage and cryotherapy are recommended. If the lesion is > 1 cm on a CT scan, resection is recommended.²¹ Unicystic lesions often require enucleation and curettage.

Multicystic lesions demand surgical intervention.² Incomplete resection often results in high rates of recurrence, which reaches up to 70%. The prognosis is poor due to its hidden nature, local aggressiveness, and the high tendency of recurrence. Prognosis is often dependent on several factors such as the patient's age, tumor sizing, tumor histology, tumor extent, and staging of the tumor.⁹ To keep track of any recurrences, patient follow-up is recommended for at least five years.¹

In conclusion, ameloblastoma is a rare, benign odontogenic tumor derived from the dental lamina, affecting mainly the jawbone. As well as being slow-growing and locally aggressive, it has a significantly high recurrence rate. Surgical excision with safety margins is the preferred treatment. Early intervention and diagnosis are crucial to better outcomes. ■

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