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Case Report

Maxillary Ameloblastoma with Local Recurrence, Orbital Invasion, and Systemic Metastases: A Case Report and Review of the Literature

Taylor J. Linaburg[a] Javiera Araya[b] César A. Briceño[a]

[a]Scheie Eye Institute, University of Pennsylvania, Philadelphia, PA, USA; [b]Orbit Unit, Department of Ophthalmology, Hospital Clínico Universidad de Chile, Universidad de Chile, Santiago, Chile

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Maxillary ameloblastoma · Orbit · Local recurrence · Metastasis · Surgery

Abstract
Introduction: Maxillary ameloblastoma is a rare, slow-growing odontogenic tumor that can recur after surgical excision, be locally aggressive, and rarely develop systemic metastases. We describe the course and management of a patient with recurrent maxillary ameloblastoma with orbital invasion and systemic metastases, the fourth case of its kind to be described in the literature. ***Case Presentation:*** A 50-year-old female presented with left hyperglobus. A diagnosis of maxillary ameloblastoma was made based on biopsy and neuroimaging with MRI and CT. Surgical management included partial maxillectomy with orbital floor reconstruction, given the orbital invasion. Three years later, left hyperglobus recurred, and the patient was found to have orbital recurrence and lung metastases on PET imaging. The lung and orbital lesions have responded well to chemoradiation therapy without surgical intervention. ***Conclusion:*** Maxillary ameloblastoma is a rare tumor that typically arises from odontogenic tissues. Though considered benign, they can recur and in the case of our patient, metastasize. Complete surgical excision with wide surgical margins is associated with a shorter average time to recurrence and a lower incidence of metastasis. Cases of metastasis are managed with chemotherapy with or without adjuvant radiotherapy. Precision medicine may play a role in managing this entity in the future, given the discovery of differing profiles of maxillary ameloblastoma compared to mandibular. Ophthalmologists should be aware of this tumor as it can invade the orbit, resulting in significant ocular morbidity and mortality.

Correspondence to:
Taylor J. Linaburg, taylor.linaburg@pennmedicine.upenn.edu

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Introduction

Ameloblastoma is an uncommon neoplasm, arising from remnants of odontogenic epithelium, lining of odontogenic cysts, and overlying oral mucosa; it comprises approximately 1% of all cysts and tumors of the jaw [1–4]. The majority of ameloblastoma tumors originate from the mandible (75–80%) and a minority originate from the maxilla (15–20%) [2–4]. Maxillary ameloblastoma often presents within the 4th or 5th decade of life. While ameloblastomas are considered histologically benign, they are aggressive with the propensity for local recurrence and invasiveness of nearby structures such as the orbit; patients with orbital involvement have a higher risk of vision loss, morbidity, and mortality [3, 5, 6]. Orbital involvement should be suspected in patients with presenting symptoms including but not limited to proptosis, decreased vision, hypoesthesia in the ophthalmic and maxillary divisions of the trigeminal nerve, diplopia, blurred vision, and limited extraocular movements [6]. Rarely, maxillary ameloblastoma can metastasize or transform into ameloblastic carcinoma, both of which are frequently lethal [3, 5–8]. Standard of care is surgical excision with negative margins, with maxillary tumors being inherently difficult to treat due to extensive disease at time of diagnosis; metastases, when present, are treated with chemotherapy [4, 5, 9, 10].

We reviewed the English literature by searching PubMed and Embase using keywords including ameloblastoma, maxilla/maxillary, ameloblastic carcinoma, odontogenic tumors, orbit, and eye. We identified 31 well-documented cases, with five publications in ophthalmologic literature, of which 23 had local recurrence and three had both local recurrence and distant metastasis (shown in online suppl. Table 1; for all online suppl. material, see https://doi.org/10.1159/000537707) [4, 6–21]. We describe the course and management of 1 patient diagnosed with recurrent maxillary ameloblastoma with orbital invasion and systemic metastasis, the fourth case reported in the literature. Written informed consent was obtained from the patient for publication of this case report and any accompanying images. We present the following case in accordance with the CARE guidelines [22]. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material.

Case Report

A 50-year-old female was referred to our institution with 3 months of left hyperglobus and paresthesias in the distribution of V2, for CT and MRI imaging concerning for mass of the left maxillary sinus with tumor visible along orbital floor with bony defect to the inferolateral orbit (shown in Fig. 1, 2). Examination was notable for visual acuity of 20/20 in both eyes, extraocular movements were full without deficits in both eyes, and there was no proptosis with exophthalmometry measurements of base 90 mm, 18 mm right eye and 18 mm left eye. Subsequent loose tooth removal and biopsy results were notable for maxillary ameloblastoma with acanthomatous and follicular patterns. She underwent left partial maxillectomy with radial forearm free flap, orbital floor reconstruction with an inert porous implant, and stenting of the nasolacrimal duct with a bicanalicular silicone stent. Histology confirmed maxillary ameloblastoma with acanthomatous and follicular patterns, with negative margins and no lymph node involvement. Postoperatively, the patient was orthotropic with full extraocular movements and normal tear lake. Three years later, the patient re-presented with recurrent left hyperglobus (shown in Fig. 1). On exam, vision was 20/20 in both eyes, and she had a mild abduction defect of the left eye without complaint of diplopia and no proptosis by exophthalmometry. MRI orbits demonstrated a new signal

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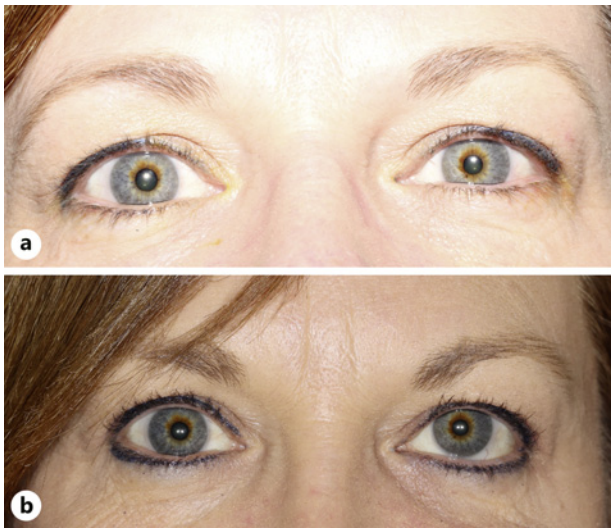

Fig. 1. Clinical pictures demonstrating subtle left hyperglobus at presentation (**a**) and at time of recurrence 3 years after initial presentation (**b**).

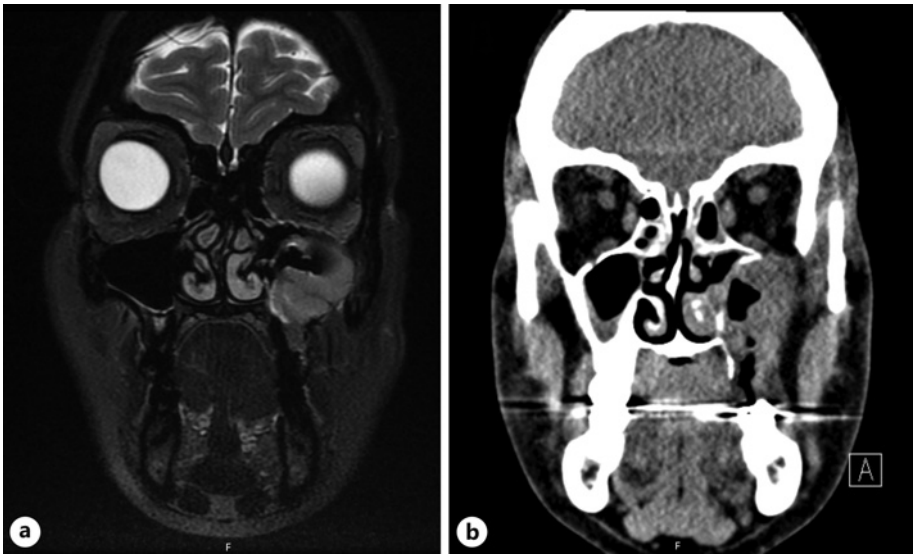

Fig. 2. Imaging at original presentation. **a** T2 MRI orbits with abnormal enhancing tissue that is T2 hypointense with restricted diffusion in the left maxilla and left maxillary sinus, consistent with neoplasm. **b** Maxillofacial CT scan demonstrates soft tissue density extending into the left maxillary sinus and correlates with enhancing tissue seen on MRI. There is associated multifocal thinning and erosion of the posterior and lateral walls of the left maxillary sinus, inferolateral left orbit, and involvement of skull base foramina without intraorbital or intracranial extension.

abnormality along the left orbital floor suspicious for recurrence, and maxillofacial CT demonstrated a slight interval increase in soft tissue mass in the left orbital floor corresponding to the area of new signal abnormality on MRI (shown in Fig. 3). Whole-body PET demonstrated local recurrence in the left orbital floor as well as FDG-avid cervical nodes and pulmonary nodules suspicious for metastatic disease (shown in Fig. 4). Biopsy of a left lower lobe lung nodule demonstrated maxillary ameloblastoma with acanthomatous and follicular patterns, confirming the diagnosis of metastasis. There were no actionable mutations found on genetic testing. She has undergone three rounds of gemcitabine/cisplatin chemotherapy,

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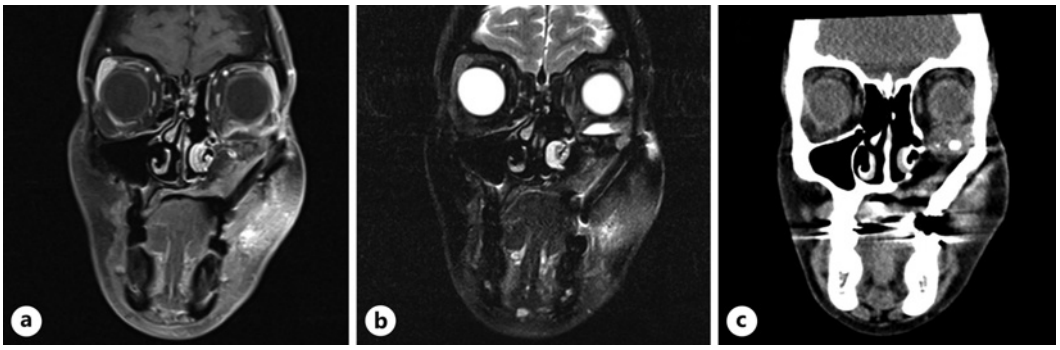

Fig. 3. Imaging at time of recurrence. T1 (**a)** and T2 (**b**) MRI orbits with and without contrast demonstrating enhancement along the left orbital floor and superolateral maxillary sinus reconstruction bed. There is superior displacement of the inferior rectus, left frontal sinus opacification, and no proptosis. **c** CT maxillofacial demonstrating slight interval increase in soft tissue along the left orbital floor in the postsurgical bed, corresponding to a new area of signal abnormality on MRI.

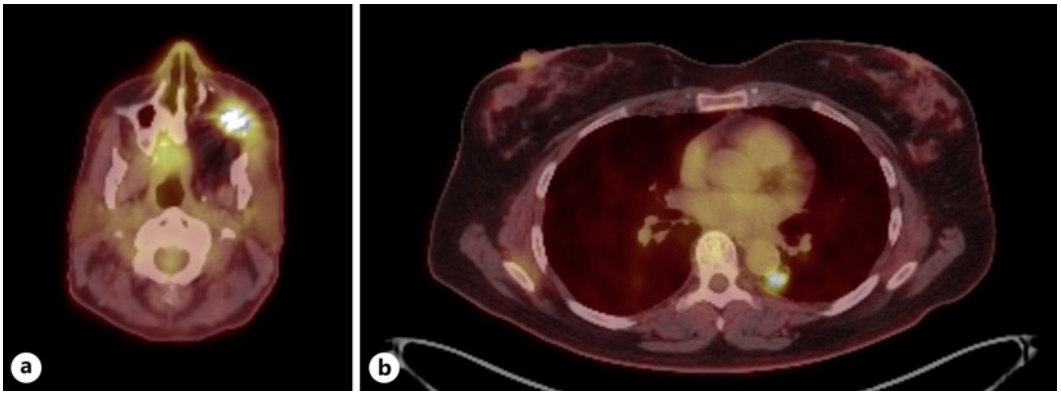

Fig. 4. PET scan at time of recurrence. **a** FDG uptake within the postsurgical bed at the left orbital floor, concerning for recurrence of ameloblastoma. **b** FDG uptake in the left lower lobe pulmonary nodule posterior to the aorta, suspicious for metastatic disease.

followed by 6 weeks of radiotherapy with weekly cisplatin to maximize local control. Posttreatment PET scans demonstrated resolution of lung nodules and a small remaining signal in the infraorbital mass, which is favored to be postsurgical changes and resolving inflammation instead of incomplete tumor response with remaining active disease. She is currently undergoing interval imaging every 3 months with PET/CT and MRI orbits of the infraorbital mass to assess for stability over time. Currently, there are no plans for further chemoradiation due to intolerable adverse effects of chemotherapy including severe ototoxicity in the setting of her favorable response. Additionally, there are no plans for further surgical procedures.

Discussion

Ameloblastoma is a rare slow-growing, histologically benign but locally invasive neoplasm of odontogenic origin [19]. It can involve the maxilla and eventually the adjacent structures such as the orbit due to the spongy, thin, and fragile architecture of the maxillary

bone, enabling easy tumor spread to surrounding vital structures [2–4]. Patients with maxillary ameloblastoma with orbital involvement present later in the 5th and 6th decades of life; this likely reflects the slow growth of this tumor despite its locally aggressive course [4–6]. Male predilection has also been reported in patients with orbital involvement [4, 6]. Several histologic subtypes of ameloblastoma have been reported including follicular, plexiform, acanthomatous, basal cell-like, desmoplastic, and granular cell [3, 4, 6]. Patterns can coexist in a tumor which is defined by the most predominant pattern present [3, 5, 23]. The most commonly encountered histologic patterns include follicular and plexiform. Several studies have noted an increased risk of recurrence in follicular ameloblastoma compared to the plexiform variant, as seen in our patient [3, 6, 23]. Though maxillary ameloblastomas are generally benign and rarely metastasize, there have been cases reported of malignant ameloblastomas with histologic atypia and distant metastasis, most commonly to the lung, also as seen in our patient [3, 4, 7, 13]. The prognosis of metastatic ameloblastoma is poor. Patients with metastatic disease survive a median of 3 years, with a 5-year survival rate of 37% [24].

In online supplementary Table 1, we detail 32 cases of orbital involving maxillary ameloblastoma, 31 from the literature and our case described. Average age at diagnosis was 50 years (range: 3.5–81 years); 25 were male (78%), and 7 were female (22%). Most common presenting signs and symptoms include facial edema (41%), decreased or loss of vision (31%), proptosis (31%), nasal congestion (22%), globe displacement (13%), and paresthesias (13%). Histologically, 44% were follicular, 28% were plexiform, 13% were ameloblastoma ex-carcinoma, and the remaining 16% other less common types or unspecified. Of the 32 cases, 41% had recurrence and 9% had distant metastases. Regarding management, 63% had surgery alone; 19% had surgery with radiation therapy; 13% had surgery, radiation, and chemotherapy; and 6% had radiation alone. Average follow-up was 9.6 months (range: 0.5–48 months). Regarding survival, 63% were alive, 31% were presumed dead or had died, and 6% were unspecified.

Milman et al. [6] reports that approximately half of the patients with maxillary ameloblastoma had recurrences greater than 5 years after initial diagnosis, and recurrences have been described to be seen as late as 33 years after initial diagnosis [3, 6]. Patients with orbital ameloblastoma have a higher risk of vision loss and mortality from local recurrence and a higher risk of developing ameloblastic carcinoma ex-ameloblastoma at a rate of 17% compared to the traditionally reported risk of two percent [5, 6]. This highlights the aggressive nature of maxillary ameloblastoma with orbital involvement and emphasizes the need for continued monitoring with clinical examinations and imaging studies in regular intervals even after treatment cessation [3, 23].

Diagnosis is made with imaging using both MRI and CT; the PET scan can be used to evaluate metastatic disease and identify alternative biopsy sites. The gold standard of treatment is complete surgical excision with negative margins [5, 25]. Total maxillectomy is recommended for tumors of the orbital floor alone, and total maxillectomy with orbital exenteration is recommended for tumors also involving orbital soft tissues, and total maxillectomy with anterior skull base resection and orbital exenteration is suggested for tumors involving the skull base [6, 25]. There are four reported cases of metastatic ameloblastoma, most commonly to the lung; prognosis is poor with a median survival of 3 years and a 5-year survival rate of 37% [3, 4, 7, 13, 24]. Reported treatment is with systemic chemotherapy with or without radiotherapy.

Surgical resection with negative margins is essential, given the high incidence of recurrence after surgical management of this entity (50–72%) [3]. Milman et al. [6] reported that patients who initially managed with conservative excision had a shorter average time to recurrence of 3.4 years compared to those who managed with maxillectomy at 4.5 years.

Preoperative MRI and CT have been recommended to evaluate the extent of soft tissue involvement, and intraoperative imaging has been advocated as a superior modality to assess surgical margins [5, 6, 26]. Ameloblastoma specimens can have 2–8 mm of microscopic extension beyond the radiographic margins, and thus, recommended surgical margins are 1–2 cm beyond radiographic margins [5]. Recently, intraoperative frozen section consultation has been advocated, though accuracy of this technique is limited by sampling and technical difficulties of performing frozen sections on bone, and the utility of this method in relation to survival remains undetermined given the short follow-up currently available within the literature for immediate assessment of tumor margins [5, 6, 26].

Data surrounding radiotherapy and chemotherapy for use as primary or adjuvant treatment of maxillary ameloblastoma are controversial, given the absence of prospective randomized studies, though most experts believe they are not effective in this setting [5, 27]. Reichart et al. [3] reported a recurrence rate with use of radiotherapy alone of approximately 70%, and cases that report use of chemotherapy with or without radiotherapy have had unfavorable outcomes, though this may be secondary to the level of advanced disease [3, 4, 6, 7, 9, 13, 16, 18, 19].

Recent studies have evaluated the mutational profile of ameloblastoma, finding that BRAF mutations are commonly found in mandibular ameloblastoma, while SMO (smoothened) mutations predominantly occur in maxillary ameloblastoma; further, SMO and BRAF mutations are nearly always mutually exclusive [5]. It is postulated that select pharmacologic inhibitors of sonic hedgehog signaling such as KAAD_cyclopamine and arsenic trioxide may be effective for patients with maxillary ameloblastoma with actionable SMO mutations, and studies are currently underway to investigate the effect of such treatments on ameloblastoma cells [5, 28]. Our patient was evaluated for actionable mutations. Unfortunately, none were identified.

Ophthalmologists should monitor patients with maxillary ameloblastoma carefully with clinical examination and imaging for early detection of recurrence. Surgical management with negative margins is preferred, and further studies evaluating the efficacy of intraoperative imaging and frozen sectioning may lead to more successful initial surgical resections and potentially shorter average time to recurrence and lower incidence of metastasis. Genetic testing should be performed to better characterize this poorly understood entity and identify actionable mutations for use of precision medicine in patients with metastatic disease.

Statement of Ethics

This retrospective review of patient data did not require ethical approval in accordance with local and national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

César Briceño, MD, had the idea for the article. Taylor Linaburg, MD, performed the literature search, data analysis, and drafted the work, and César Briceño, MD, Taylor Linaburg, MD, and Javiera Araya, MD, critically revised the work.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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