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Review

Orbital invasion of ameloblastoma: A systematic review apropos of a rare entity

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Abstract

Purpose: Ameloblastoma is a non-encapsulated and slow-growing tumor with high recurrence rate. Orbital involvement by this neoplasm is an extremely rare entity. In this study, we present a systematic review on this situation along with clinical and paraclinical features of a case.
Methods: An electronic search was conducted on major medical sources. Data of the cases in the literature in addition to our own case were extracted, summarized, and statistically analyzed.
Results: A total of 36 other cases from 20 relevant studies were also reviewed. Review topics included epidemiology, clinical presentation, pathologic features, differential diagnosis, imaging, treatment, and prognosis. We provided a five-year history of a 50-year-old man with orbital/skull base invasion of plexiform maxillary ameloblastoma.
Conclusions: Maxillary ameloblastoma is a locally aggressive neoplasm, and physicians must be alert to the biologic behavior of this tumor to detect any invasion to critical structures such as orbit and cranium. Orbital ameloblastoma causes significant morbidity and mortality. We advocate meticulous patient follow-up with regular clinical examinations and paraclinical work-up for timely detection of any invasion or recurrence. The best must be done to avoid extensions by aggressive removal of maxillary ameloblastoma.

Keywords: Ameloblastoma; Eye; Vision; Orbit; Review

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Introduction

Ameloblastoma is a non-encapsulated, slow-growing tumor with high recurrence rate.[1–3] This neoplasm was first described in 1879 by Folkson, and the term 'Ameloblastoma' was first used by Churchil in 1933.[4] In the literature, there are some other terms used interchangeably with ameloblastoma such as 'cystosarcoma', 'adamantine epithelioma' and 'adamantinoma'.[5]

The origin of tumor is known to be remnants of odontogenic epithelium, lining of odontogenic cysts, and overlying mucosa.[1–3] The tumor arises from the mandible in approximately 80% of cases, mostly in association with an unerupted tooth. In addition, it may arise from the tuberosity of maxillary sinus in approximately 20% of cases.[6–8] Demographically, the reported age range of cases varies from 20 to 50 years with no sexual preponderance. Ameloblastoma rarely invades the orbit; if it does, it involves the orbit in the elderly with male predilection.[9]

Ameloblastoma is reported to be the most prevalent odontogenic tumor in our country, Iran.[10] However, to the best of our knowledge, there is no report of its invasion to the orbit either by the authors from Iran or other parts of the Middle East. The purpose of the study was to present the clinical and paraclinical features of a patient suffering from orbital ameloblastoma and an outline on previous reported cases. For the first time, we provide a systematic review on epidemiology, clinical aspects, pathology, prognosis, and current treatment modalities of this situation.

Methods

For the literature review process, a thorough electronic search was performed on the PubMed, Medline, Scopus, EMBASE, and web of science databases using the following keywords and terms: 'ameloblastoma', 'odontogenic tumors', 'orbital', 'ocular', 'eye', 'vision', and 'ophthalmic'. A reference list of eligible articles was also reviewed for possible eligibility. No limitation on publication date, study type/design, and language was applied.

Data of the cases in the literature in addition to our own case were further extracted and summarized based on the following items including age, sex, histopathology, initial location of the tumor, sites of extension, ophthalmologic sign and symptoms, management, recurrence, outcome, and disease duration. Furthermore, extracted data were descriptively analyzed in different histopathological categories for the following variables: age, age at diagnosis of ameloblastoma, origin, delay between diagnosis to invasion, location of extension, main ophthalmic presentation, delay between the last therapeutic modality and the date of recurrence and survival. Results were reported as mean ± standard deviation, maximum and minimum values, mode, median, and/or number (percent). Descriptive data analyses were conducted by IBM SPSS version 21.0 software (SPSS, Inc, Chicago, IL).

The study protocol and patient's ophthalmologic visits as well as orbital procedures were performed at Feiz Eye Hospital, located in Isfahan city, in the center of Iran. This university hospital serves as the referral center for at least four adjacent provinces. Our patient signed an informed consent for the publication of his disease data.

Results

Until now, thirty-seven (including our patient) cases with orbital invasion of ameloblastoma have been described in the literature. Previously, it has been proposed that ameloblastoma invades the orbit in 5th–6th decade of life[11]; in our literature review, the mean age of patients with orbital invasion of ameloblastoma was 52.79 ± 20.62 years, ranging from 7 to 81. Interestingly, the mean age of patients varied in different patterns; 51 ± 20.45 years in follicular; 59.5 ± 9.2 years in mixed; 62.8 ± 18.8 years in plexiform, and 63 ± 0.0 years in basal cell-like pattern. Furthermore, similar to other reports,[12,13] we found male preponderance, and the male to female ratio was 2.8:1. In none of the reported patients ameloblastoma developed primarily in the orbit, and all of the cases were secondary due to invasion from either maxillary or mandibular sinuses. The mean delay from onset of disease to orbital invasion was 12.7 ± 13.7 years. The mean delay of invasion varied in different patterns: 17 ± 16.9 years in follicular and 12.33 ± 15.37 years in plexiform. Almost always, invasion occurs unilaterally; however, two cases with bilateral invasion of tumor have been described.[12,14] The most common pattern of neoplasm was follicular followed by plexiform; however, the most prevalent tumor pattern in males and females were plexiform and follicular, respectively. According to patients' histories, the most common complaint at disease onset was decreased or loss of vision followed by proptosis. Most of the patients were managed surgically with or without chemotherapy or radiotherapy, and the mean age of survival was 13.47 ± 12.81 years.

In the literature, we found 20[1,11–29] studies describing 36 individuals with orbital invasion of ameloblastoma. The article publication dates ranged from 1934 to 2017. Table 1 shows age, sex, histopathology, initial location of tumor, sites of extension, ophthalmological signs and symptoms, management, recurrence and outcome of reported cases. Data of patients are further analyzed in Table 2.

Case Report

A 50-year-old man was referred to the oculoplastics service at the Feiz Eye Hospital in January 2014 for the evaluation of progressive inferior lid swelling and diplopia in down gaze. He was visited by a dentist in March 2011 for the extraction of upper third molar tooth. Two weeks following the extraction, a blister in his lingual vestibule adjacent to the extraction site appeared. The dentist evacuated the blister fluid with a surgical blade. Two weeks later, the patient was referred to a maxillofacial surgeon for the recurrence of the blister and computed tomography (CT) in April 2011, showing a mass in the maxillary sinus. At that time, the tumor was resected so that pathologic assessment revealed the diagnosis of plexiform ameloblastoma. Six months later in November 2011, the tumor

Table 1
Demographical and clinical features of patients with orbital ameloblastoma.

Author[Ref.] (Country; year of report; no. of cases)	Age	Sex	Histopathology	Initial location of tumor	Sites of extension	Ophthalmologic signs and symptoms	Management[a]	Recurrence[b]	Outcome, disease duration (years)
O'brien and leinfelder[11] [USA, 1934, 1]	7	N/A	N/A	Maxilla	Nasal margin of orbit, sphenoid wing	Proptosis, lateral and upward globe displacement, upward gaze limitation	N/A	N/A	N/A
Linnert[12] [U/A, 1970, 1]	N/A	N/A	N/A	N/A	Orbit	N/A	N/A	N/A	N/A
Kyriazis et al.[13] [USA, 1971, 1]	73	F	Ameloblastic carcinoma, ex-Follicular	Maxilla	Orbit (bilateral), ipsilateral middle cranial fossa, ipsilateral temporal lobe, petrous apex (bilateral), BOS	Bilateral visual loss	Partial maxillectomy (0), WLE (3 and 5)	N/A	Passed away, 8
Spaeth[14] [U/A, 1971, 1]	N/A	F	N/A	Maxilla	Orbit	N/A	N/A	N/A	N/A
Shaw and Katsikas[15] [UK, 1973, 2]	81	M	Plexiform	Maxilla	Orbit	Deterioration of vision, proptosis, lower lid edema	50 Gy RT	N/A	Passed away, 4
	77	F	Follicular	Maxilla	Orbit	Proptosis, globe displacement, lower lid edema	RT and conservative resection (0), partial maxillectomy (2)	recurrence occurred (3.5 years)	N/A
Tsakins and Nelson[16] [U/A, [1980, 1]	N/A	N/A	N/A	Maxilla	Orbit	Decreased VA	N/A	N/A	N/A
Daramola et al.[17] [USA/1984, 1]	22	M	Follicular	Maxilla	Orbit, frontal sinus, pulmonary metastasis	No visual complication	WLE (0), total maxillectomy (3), 36 Gy RT, chemotherapy (5)	N/A	Passed away, 5
Komisar et al.[18] [USA, 1984, 1]	63	M	Plexiform	Maxilla	Orbit, BOS, pterygoid plate, infratemporal fossa	No visual complication	Curettage (0), total maxillectomy (2)	Recurrence occurred (1 year)	Passed away, 3
Weiss et al.[19] [USA, 1985, 1]	72	M	Plexiform	Maxilla	Orbit, middle cranial fossa	Decreased VA, proptosis, EOM limitation	WLE (1), Partial maxillectomy (2), RT (5), radical maxillectomy, ethmoidectomy, sphenoidectomy, orbital exenteration (5.5)	N/A	Passed away, 7
Bredenkamp et al.[20] [U/A, 1989, 4]	53	M	Mixed	Maxilla	Orbit, cavernous sinus, middle cranial fossa, BOS	Proptosis, decreased VA	RT	N/A	Survived, 1
	15	M	Plexiform	Maxilla	Orbit, middle cranial fossa, BOS	No visual complication	Maxillary tumor enucleation (0), radical maxillectomy, orbital exenteration (2), RT (4), chemotherapy (8), debulking (8−14)	N/A	Passed away, 15
	37	F	Follicular	Maxilla	Orbit, palate, nasopharynx, BOS, internal carotid	Visual loss, globe displacement	Curettage (0), partial maxillectomy (1), RT (2), complete maxillectomy (7), multiple WLE (8)	N/A	Passed away, 8
	43	M	Follicular	Maxilla	Orbit, nasopharynx, palate, sphenoid sinus, BOS	No visual complication	Total maxillectomy (0), WLE (3), repeated cryotherapy (4−11)	N/A	Passed away, 11

(*continued on next page*)

Table 1 (*continued*)

Author[Ref.] (Country; year of report; no. of cases)	Age	Sex	Histopathology	Initial location of tumor	Sites of extension	Ophthalmologic signs and symptoms	Management[a]	Recurrence[b]	Outcome, disease duration (years)
Moster et al.[21] [U/A, 1991, 1]	37	F	N/A	Mandible	Orbit, cavernous sinus, sella, suprasellar	Cavernous sinus syndrome, visual loss, complete EOM limitation, ptosis, absent corneal reflex	RT	Recurrence occurred (4 months)	Passed away, <1 (due to meningitis)
Henderson et al.[22]	21	M	N/A	Maxilla	Orbital floor, ethmoid sinus	N/A	N/A	N/A	N/A
[U/A, 1994, 3]	58	M	N/A	Maxilla	Orbit	N/A	N/A	N/A	N/A
	63	M	N/A	Maxilla	Orbit	N/A	N/A	N/A	N/A
Sato et al.[23] [Japan, 1994, 1]	68	M	Follicular	Maxilla	Anterior cranial fossa, middle cranial fossa, orbital	Proptosis, diplopia (9) painful progressive swelling mass in orbit	Radical maxillectomy (2), debulking (9), orbital exenteration (10), craniotomy and debulking (11)	N/A	Survived, 12
Brazis et al.[24] [USA, 1995, 3]	43	M	N/A	Mandible	Orbit, superior orbital fissure, cavernous sinus	Visual loss, impaired ocular motility, orbital apex, cavernous sinus syndrome	Curettage (0) resection (4) radical surgery of left maxillectmy, mandibular ramus and pharyngeal muscles (9), combined left orbit/intracranial exploratin (10.5), left cranitomy (11)	recurrence occurred (6 months)	Survived, 10
	11	F	Follicular	Maxilla	Orbits (bilateral), infratemporal fosse (bilateral), cavernous sinuses (bilateral), ipsilateral sphenoid and ethmoid sinuses, ipsilateral anterior cranial fossa, BOS (bilateral)	Bilateral visual loss, impaired ocular motility, exposure keratopathy	Cactus planet (0), resection (5), several operations and RT (11−19), left hemiadenectomy and partial maxillectomy (32),	Recurrence occurred (4.5 months)	Passed away, 48
	33	M	N/A	Maxilla	Infratemporal and middle cranial fossa, orbit, cavernous sinus	Esophoria	Radical maxillectomy, cryotherapy, sphenoethmoidectomy	Recurrence occurred (4 months)	Survived, 20
Hayashi et al.[25] [Japan, 1997, 1]	63	F	Ameloblastic carcinoma, ex-follicular	Mandible	Orbit, extramandibular tissue (note noted), intracranial space, frontal region	Decreased VA, central scotoma, anisocoria	Multiple excision, RT (29 Gy), chemotherapy	Recurrence occurred (6 months)	Survived, 28
Zwahlen and Grätz[1] [Switzerland 2002, 1]	44	M	Follicular	Maxilla	Orbit, orbital soft tissue, mandible, extensive BOS infiltration, optic chiasm, lung and heart metastases	Proptosis, diplopia, decreased VA	En bloc resection (0), partial maxillectomy, ethmoidectomy (6), radical maxillectomy, sphenoidectomy (8), RT (9), palliative debulking (11−13)	Recurrence occurred (1 month)	Passed away, 13
Leibovitch et al.[26] [USA, 2006, 2]	60	M	Follicular	Maxilla	Orbital soft tissue	Diplopia, globe displacement, decreased VA	Partial maxillectomy, RT (0), orbital exenteration, partial zygomatic bone resection (3)	Recurrence occurred (1.5 years)	Survived, ~5
	73	M	Plexiform	Maxilla	Middle cranial fossa, temporal area, orbital soft tissue	Diplopia, globe displacement, decreased VA	Multiple resections (0−30), BOS and orbital tumor resection (30)	Recurrence occurred (6 months)	Survived, ~30.5
Herwing et al.[27] [USA, 2013, 1]	66	M	mixed	Maxilla	Orbit, BOS, paranasal sinuses, nasopharynx	Proptosis, globe displacement, decreased VA	Multiple resections, RT, brachytherapy	N/A	N/A

Milman[28] [USA, 2015, 8]	67	M	Plexiform	Maxilla	Nasopharynx, orbital floor	No visual complication	Radical maxillectomy, BOS resection, FESS (0)	Recurrence occurred (6 years)	N/A
	73	M	Ameloblastic carcinoma, ex-plexiform	Maxilla	Nasopharynx, orbital floor	No visual complication	Total maxillectomy, BOS resection, RT (0)	Recurrence occurred (2 years)	N/A
	71	M	Follicular	Maxilla	Orbital floor, nasolacrimal duct	No visual complication	Conservative resection (0, 9, 14), partial maxillectomy (20), FESS(27)	Recurrence occurred (30 years)	N/A
	73	M	Plexiform	Maxilla	Nasopharynx, orbital floor	No visual complication	Total maxillectomy, BOS resection (0)	Recurrence occurred (1 year)	N/A
	63	M	Basal cell-like	Maxilla	Nasopharynx, orbital floor	No visual complication	Total maxillectomy, BOS resection, turbinectomy (0)	Recurrence occurred (6 months)	N/A
	61	M	Plexiform	Maxilla	Orbital floor	No visual complication	Total maxillectomy, BOS resection (0)	Recurrence occurred (6 months)	N/A
	63	F	Ameloblastic carcinoma, ex-basal cell-like	Maxilla	Orbital floor, zygoma, orbital soft tissue, temporal dural mandible	N/A	Partial maxillectomy (0), wide resection (4), BOS resection, orbital exenteration (5), total mandibulectomy, neck dissection (7)	Recurrence occurred (9 years)	N/A
	38	M	Follicular	Maxilla	Orbital floor, orbital soft tissue	Proptosis	Conservative resection (0), partial maxillectomy (1), ethmoidectomy (2), orbital floor resections (8, 10, 18), orbital soft tissue resection (24)	Recurrence occurred (31 years)	N/A
Faras et al.[29] [France, 2017, 1]	56	F	Follicular	Mandible	Maxillary sinus, zygomatic arch floor of orbit, external wall of left eye	N/A	Hemimandibulectomy (31), surgical excision (12), two surgical excision (12), surgical excision (2), surgical excision (0)	N/A	Survived, 31
Abtahi et al. [Iran, 2016, 1]	50	M	Plexiform	Maxilla	Orbit, BOS	Decreased VA, proptosis	Conservative resections (0) total maxillo palatectomy (1), orbital floor resection (3)	Recurrence occurred (4 months)	Survived, 5

M: Male, F: Female, N/A: Not Available, WLE: Wide local excision, BOS: Base of skull, VA: Visual acuity, FESS: Functional endoscopic sinus surgery, GY: Gray, RT: Radiation Therapy, EOM: Extraocular movement.

[a] Values presented through (*parenthesis*) in this column denote the years of follow-up passed when each therapeutic modality is applied.

[b] Values presented through (*parenthesis*) in this column denote the years or months of follow-up passed until a recurrence occurred.

Table 2
Analyzed data of patients with invasive orbital ameloblastoma.

		Histopathology				
Orbital ameloblastoma	Total N = 37 F:M = 9:25	Follicular N = 13 F:M = 6:7	Plexiform N = 10 F:M = 0:10	Basal cell-like N = 2 F:M = 1:1	Mixed N = 2 F:M = 0:2	Not available N = 10 F:M = 1:7
Age (years)	N = 34 52.9 ± 20.3 (7, 81, 63, 60.5)	N = 13 51 ± 20.4 (11, 77, 11a, 56)	N = 10 62.8 ± 18.8 (15, 81, 73, 69.5)	N = 2 63 ± 0.0 (63, 63, 63, 63)	N = 2 59.5 ± 9.2 (53, 66, 53, 59.5)	N = 7 37.4 ± 19.7 (7, 63, 7, 37)
50 years old	N = 12	N = 6	N = 1	N = 0	N = 0	N = 5
50 years old	N = 22	N = 6	N = 9	N = 2	N = 2	N = 2
Origin						
Maxilla	N = 30	N = 11	N = 10	N = 2	N = 2	N = 5
Mandible	N = 4	N = 2	N = 0	N = 0	N = 0	N = 2
Age at diagnosis of Ameloblastoma	N = 12 42.7 ± 20.4 (7, 73, 43, 43)	N = 5 43 ± 21.8 (11, 68, 11a, 44)	N = 3 59.0 ± 15.1 (43, 73, 43, 61)	N/A	N/A	N = 4 30.0 ± 15.9 (7, 43, 7, 35)
Delay between diagnosis to invasion	N = 12 12.7 ± 13.7 (0.1, 44, 0.1, 7.5)	N = 5 17 ± 16.9 (3, 44, 3, 9)	N = 3 12.3 ± 15.4 (2, 30, 2, 5)	N/A	N/A	N = 4 7.5 ± 8.8 (0.1, 19, 0.1, 5.5)
Location of extension		Skull base, orbital soft tissue, floor and external wall of orbit, zygomatic arch, maxillary sinus, optic chiasm, frontal sinus, temporal lobe, petrous apex, infratemporal, nasopharynx, nasolacrimal, sphenoid sinus, internal carotid, palate, cavernous sinus, heart and lung	Middle cranial fossa, nasopharynx, Skull base, infratemporal fossa, pterygoid plate, orbital soft tissue, temporal fossa and petrous apex	Orbital floor, zygoma, orbital soft tissue, temporal dural, Nasopharynx	Base of skull, cavernous sinus, middle cranial fossa, BOS, paranasal sinuses, nasopharynx	Cavernous sinus, Nasal margin of orbit, sphenoid wing, sella, suprasellar, orbital floor, ethmoid sinus, superior orbital fissure, infratemporal fossa, middle cranial fossa
Main ophthalmologic presentation	Decreased or loss of vision and proptosis	Decreased or loss of vision, proptosis	Decreased visual acuity, proptosis	N/A	Decreased visual acuity	Upward gaze limitation
Delay between last therapeutic action to recurrence (year)	N = 19 4.7 ± 9.4 (0.1, 31, 0.5, 0.5)	N = 7 9.6 ± 14.3 (0.1, 31, 0.1, 1.5)	N = 7 1.6 ± 2.0 (0.3, 6, 0.5a, 1)	N = 2 4.7 ± 6.0 (0.5, 9, 0.5a, 4.7)	N/A	N = 3 0.4 ± 1.0 (0.3, 0.5, 0.3, 0.3)
Survival[a] (year)						
<0.5	13.5 (20/20, 100%)	13.5 (10/10, 100%)	10.7 (6/6, 100%)	N/A	1 (1/1, 100%)	10.3 (3/3, 100%)
1	14.1 (19/20, 95%)	13.5 (10/10, 100%)	10.7 (6/6, 100%)	N/A	0%	15 (2/3, 66%)
5	19 (13/20, 65%)	19.9 (8/10, 80%)	17.5 (3/6, 50%)	N/A	0%	15 (2/3, 66%)
10	23.7 (9/20, 45%)	23.8 (5/10, 50%)	22.7 (2/6, 33.33%)	N/A	0%	15 (2/3, 66%)

M: Male, F: Female, N/A: Not available, BOS: Base of skull.
Notes: Data presented as mean ± standard deviation (lower range, upper range, mode, median). The number of available specimens in each calculation is presented as N.
"a" in front of modes means that multiple modes exist, the smallest value is shown.
[a] Survival data presented as: Mean of survival years (Number of cases/total available cases, Percent).

recurred as a brown bulging mass at the former site. The same maxillofacial surgeon resected the tumor under general anesthesia. In May 2012, the tumor recurred with bulging of the cheek and involvement of hard palate in the maxillary region. Another maxillofacial surgeon performed total maxillectomy to handle the situation. The patient had no symptom of recurrence until his admission to our service.

In our primary inspection in 2014, the swelling was immobile without tenderness or erythema. In the ophthalmologic examination of both eyes, the best corrected visual acuity was 20/20 with normal color vision perception. Red reflex was normal. Refraction results were plano in both eyes. Ocular motility was unremarkable except the mild limitation of the down-gaze of the right eye. Proptosis was not prominent. No relative afferent pupillary defect (RAPD) was detectable. In slit-lamp examination, neither conjunctival hyperemia nor chemosis was seen. Anterior and posterior chamber examinations were unremarkable. History of trauma was negative.

According to the past history of ameloblastoma, we suspected the recurrence of the malignancy. In the magnetic resonance imaging (MRI) and CT scan, an extraconal mass in the inferior and retrobulbar areas of the orbit was notable. Inferior wall of the orbit was absent due to previous total maxillectomy. In radiologic consultation, orbital fat was reported to be intact, but periosteum involvement was reported to be probable (Figs. 1 and 2).

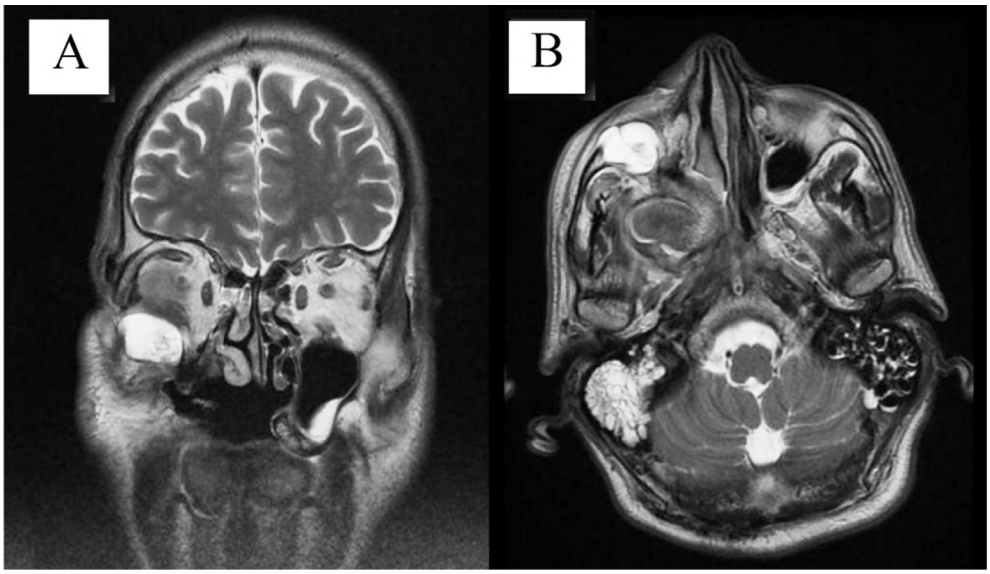

Fig. 1. T2 Magnetic resonance imaging (MRI) in January 2014: A: Coronal view showing a round enhanced mass in the inferior orbit. B: Axial view.

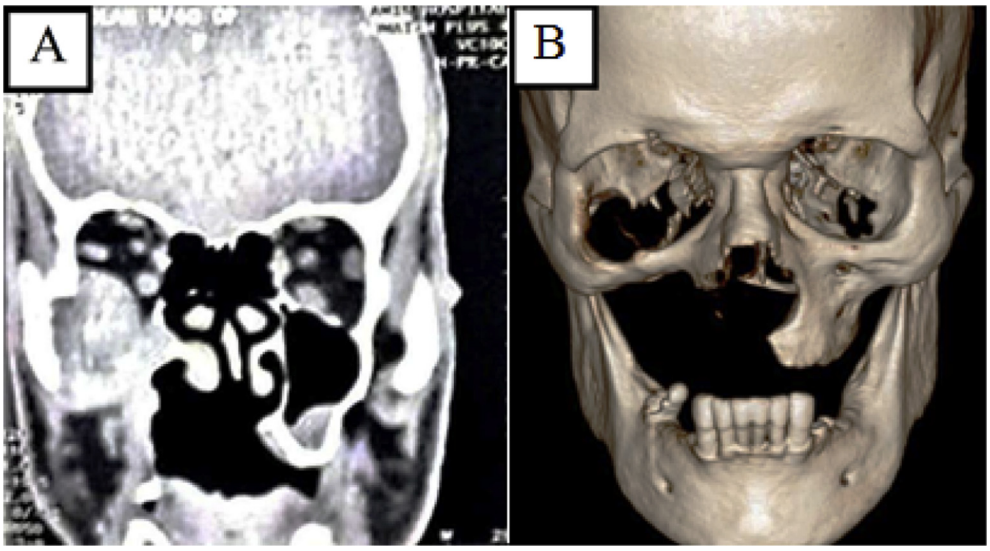

Fig. 2. A: Computed tomography (CT) scan in January 2014; B: Three-dimensional reconstruction image.

After all possible options were fully discussed, including the possible need for orbital exenteration, the patient rigorously refused exenteration and selected inferior orbitotomy. In the operating theatre, a large round solid-cystic mass with a pseudocapsule was found. Periosteum involvement could be identified; however, based on the patient's choice, orbital exenteration was avoided. The tumor was excised as much as possible with grossly free margins. The cyst content was aspirated and serosanguineous fluid (Fig. 3). Pathologic assessment of mass wall re-confirmed the diagnosis of plexiform ameloblastoma (Fig. 4). The operation was accomplished without any complication, and the postoperation period was uneventful.

Despite our strong recommendations, the patient refused to attend any of our planned radiologic reassessments and visits. He did not consent to be evaluated or treated by any means, including radiotherapy due to exhaustion of multiple surgeries as he mentioned in our phone calls.

Finally, in February 2016, the patient returned with decreased vision of right eye. In the examination, the tumor grossly recurred and caused right eye proptosis and swelling of right cheek (Fig. 5). Hyposensation of V2 branch was prominent. He seemed to be deeply depressed, suffering from depression mood disorder as reported in psychiatric consultation. In ocular examination, the right eye had a 5-mm proptosis with the best corrected vision decreased to 40/200. RAPD was 2 + in the right eye. His refraction showed 2 diopters of hyperopic shift. In the posterior segment examination, swollen optic disc and remarkable choroidal folds were presented (Fig. 6). The left eye examination was

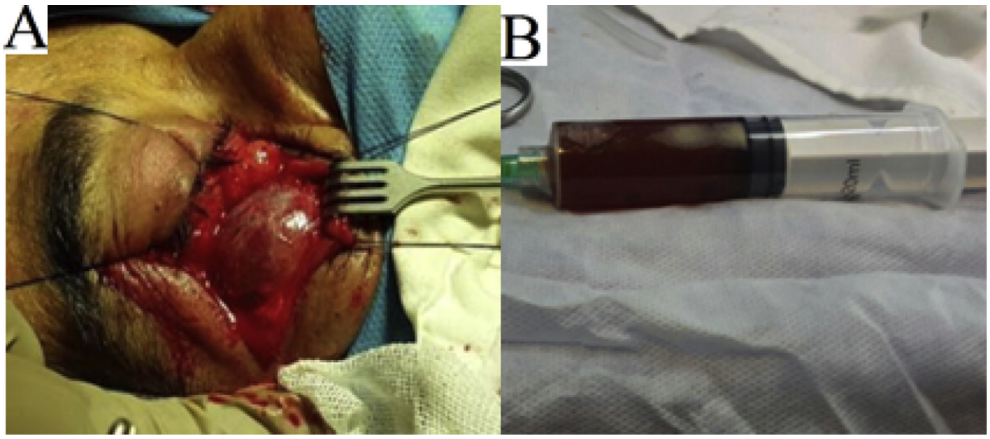

Fig. 3. A: large mass in the inferior orbit. B: Content of the cyst was serosanguineous fluid.

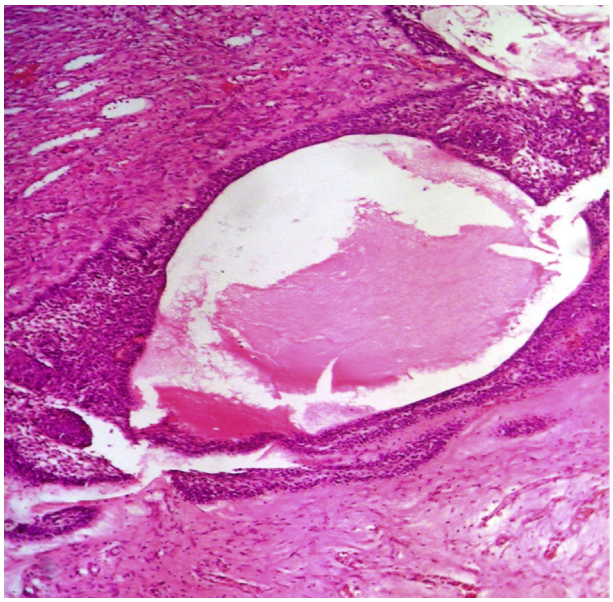

Fig. 4. Biopsy of the mass wall (H&E): Appearance of plexiform ameloblastoma; Epithelial islands surrounded by fibrous connective tissue; Center of islands consists of loose stellated epithelium cells and microcyst formation (×100).

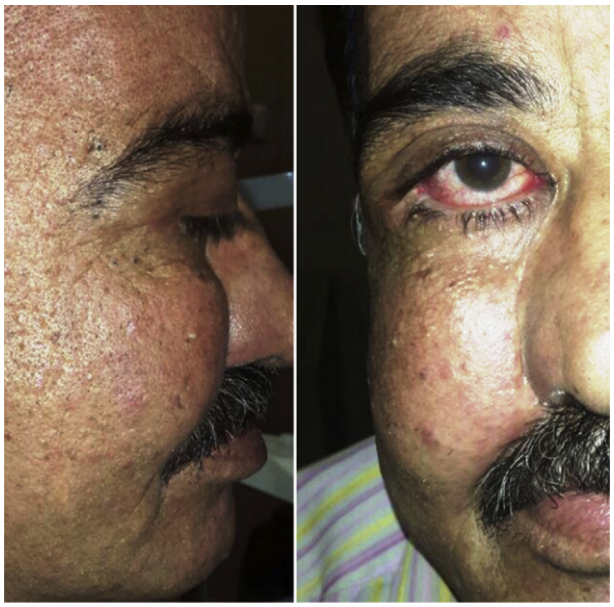

Fig. 5. Patient's appearance at his last visit; February 2016.

unremarkable. Due to imaging evidence supporting skull base involvement (Fig. 7), we referred the patient for neurosurgical consultation. They planned tumor debulking. To date (September 9, 2016), however, patient has refused to do so.

Discussion

Epidemiology

Maxillary ameloblastoma is a rare tumor known to be slow-growing and highly recurrent with a locally invasive nature.[2,3] In the United States, ameloblastoma accounts for 1% of all tumors/cysts of jaw, 1% of all head and neck neoplasms, and 10% of all tumors arising from mandible or maxilla.[1,30,31] It accounts for 9–11% of all odontogenic tumors with an incidence rate of 0.5 cases per-million.[5]

Ameloblastoma is the most common odontogenic tumor in Iran, similar to what is reported in China, Japan, and Africa, accounting for 62.2% of all such tumors.[10,32–34] Among all races, the Afro-Caribbean population is presumed to have the highest susceptibility.[30]

Regarding the demographic features, odontogenic ameloblastoma is a tumor of all ages ranging from 2 to 93 years old (mean: 39 years). Most of the mandibular and maxillary ameloblastomas occur in the 3rd–4th and 4th–5th decades of life, respectively. This difference in age at onset may be explained by the delayed diagnosis of maxillary tumor due to the spongy structures allowing the tumor to enlarge subclinically.[1,2,5]

In anecdotal postulations, ameloblastoma invades orbit more frequently in the 5th–6th decades of life.[11] Comparatively, in the data we ascertained from the literature (Table 2), the age of orbital invasion ranges from 7 to 81 years (mean: 52.79 ± 20.62 years). Among different patterns, the mean age varied from 51 ± 20.45 years to 63 ± 0.0 years. The mean

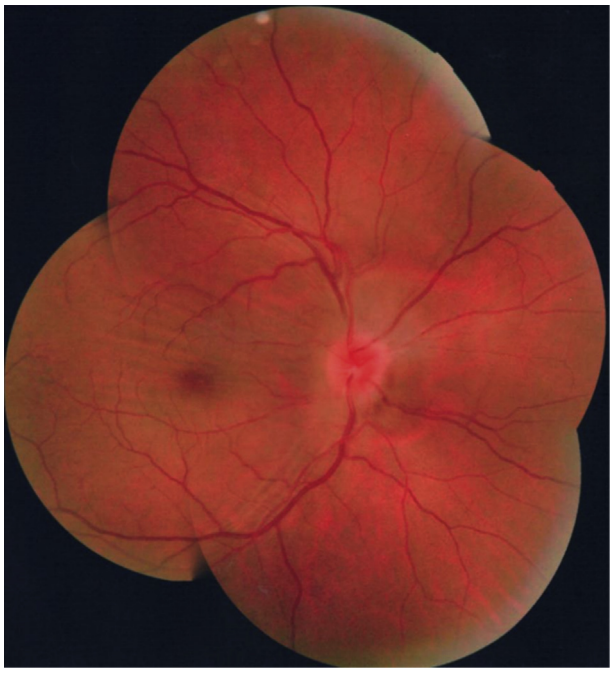

Fig. 6. Fundus photograph of the right eye shows remarkable choroidal folds and disc swelling.

delay from onset to orbital invasion was 12.7 ± 13.7 years varying among different pathologies: in follicular, 17 ± 16.9 years and in plexiform, 12.33 ± 15.37 years.

Although odontogenic ameloblastoma does not show gender predilection, most cases of maxillary ameloblastoma are male.[12] Previously, it was reported that male/female ratio of orbital invasion was 2.4:1.[13] Comparatively, in our literature review, the male/female ratio was 2.8:1.

Clinical presentation

In the literature, primary orbital ameloblastoma has never been reported; all cases were secondary to invasions from mandible or maxilla. The clinical picture of ameloblastoma depends on the origin of the tumor and also the structures involved. The most common manifestation of mandibular type is painless swelling of jaw, whereas, primary maxillary ameloblastoma presents with swelling of cheek, gingiva, hard palate, nasal obstruction, and epistaxis.[12,35] The tumor inherently invades local adjacent structures such as paranasal sinuses, orbit, and cranial fossa.[12] Invading or compressing the neurovascular structures within orbit and cavernous sinus leads to various ophthalmologic manifestations such as loss or decrease of vision as the most common symptom (15/30; 50%) followed by proptosis (10/30; 33%) and globe displacement (6/36; 20%), extraocular movement limitation (5/30; 20%), diplopia (4/30; 13%), cavernous sinus syndrome (2/30; 7%), lower lid edema (2/30; 7%), and ptosis (1/30; 3%) (Table 2). It should be noted that orbital manifestations were almost unilateral; however, there were two reports by Kyriazis et al.[14] and Brazis et al.[12] with bilateral orbital involvement.

Although, it is generally known that ophthalmologic symptoms secondary to ameloblastoma are limited to tumors of maxillary origin, in our literature review, there are some reports of ophthalmic manifestations by mandibular ameloblastoma.[12,24,26] From all the cases, orbital ameloblastoma originated from maxilla in 32 cases (88.89%), among which two had concomitant invasion to mandible and also the skull base. Interestingly, in 4 cases (11.11%), the orbital ameloblastoma originated from mandible, where invasion to the intracranial structures was also reported.

It is presumed that ameloblastic carcinoma constitutes 2% of all ameloblastoma cases.[12] In a review article, it has been proposed that ameloblastic carcinoma ex-ameloblastoma is more prevalent (17%) among cases with orbital invasion.[5] In our review on all the reported cases, ameloblastic carcinoma developed in 4 patients (11.1%), three of whom were female. This can be explained by the notion that long-standing and recurrent ameloblastoma is more likely to involve the orbit and concurrently, may transform more to aggressive ameloblastic carcinoma.[12,14,26]

Pathologic features

Several histologic types of ameloblastoma are described in the literature including plexiform, follicular, basal cell,

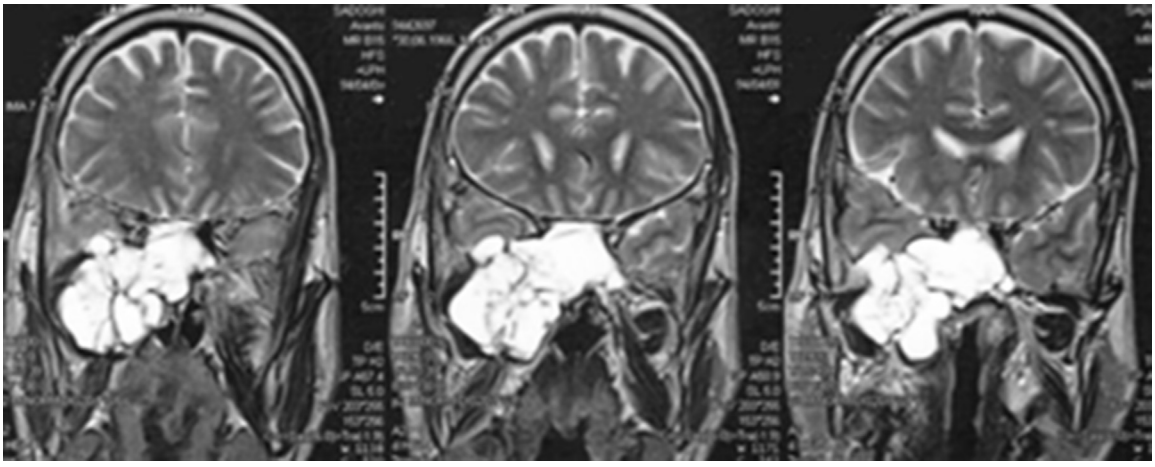

Fig. 7. Last patient T2 Magnetic resonance imaging (MRI) shows the involvement of the skull base.

granular cell, clear cell, and acanthomatous. The plexiform and follicular types are the most common patterns.[2,5] In the plexiform pattern, the connective tissue is surrounded by epithelial components while in the follicular pattern, the epithelium is surrounded by the connective tissue.[30] The basal cell-like pattern is apparently benign and tends to grow in an island-like pattern. The basaloid appearing cells tend to stain basophilic deeply. The cells in the central portion may be polyhedral to spindle shaped; stellate reticulum-like areas are notably absent.[36] It is reported that tumors with follicular and acanthomatous histology have the highest and lowest recurrence rates, respectively.[2]

In our literature review, the most common pattern of orbital ameloblastoma was follicular (13/27; 48.1%), followed by plexiform (10/27; 37%), basal cell-like (2/27, 7.4%), and mixed (2/27; 7.4%). In males, the most common tumor pattern was plexiform (10/20; 50%), followed by follicular (7/20; 35%), mixed (2/20; 10%), and basal cell-like (1/20; 5%). In females, the most prevalent type was follicular (6/7; 85.7%) followed by basal cell-like (1/7; 14.3%). Plexiform pattern was not reported in female cases (Table 2).

The causative mutation leading to ameloblastoma is the activation of FGFR2, BRAF, and RAS that can lead to the dysregulation of the MAPK signaling as a pivotal step in the pathogenesis of the tumor.[37] It seems that different mutations are involved in maxillary and mandibular ameloblastoma, and this may partially explain the higher aggressive behavior of the maxillary type. McClary et al. in their review, proposed that specifically smoothened (SMO) and RAS were the most prevalent mutated genes in maxillary ameloblastoma, while, BRAF was the most one in the mandibular counterpart.[5]

Differential diagnosis

Differential diagnosis of orbital ameloblastoma includes reactive, benign, and malignant lesions including osteomyelitis, cystic fibrous dysplasia, giant cell tumor, ossifying fibroma, multiple myeloma, and sarcomas. Generally, clinical, gross, microscopic, and immunohistochemistry features provide sufficient clues in the discrimination of ameloblastoma from other lesions.[38]

Imaging

Ameloblastomas originated within bone are mostly diagnosed incidentally in pan-tomography imaging or plain films. The routine radiographic picture is the ‘soap bubble’ appearance.[39] Plain X-ray imaging has limited sensitivity and specificity to evaluate tumor invasion. CT can be useful in detecting bone extensions, and MRI provides better resolution in detecting soft tissue extensions and tumor margins, particularly in maxillary ameloblastoma.[40] Particularly, in diagnosing the desmoplastic type, the MRI plays a pivotal role due to poor defined soft tissue extensions in addition to the similarity to fibro-osseous lesions.[41]

Treatment

In treating ameloblastoma, the mainstay is radical surgery including en-bloc resection.[5] Concerning the management of mandibular ameloblastoma, some authors maintain that partial resection or curettage is enough while many recommend radical excision. This inconsistency comes from easier follow-up and lower invasion risk of mandibular type to vital structures.[2,5]

In the maxillary type, morphology, histopathology, and extension of the tumor are crucial indecision-making. The recommended safe margin for unicystic ameloblastoma, multicystic ameloblastoma, and ameloblastic carcinoma is proposed to be 1–1.5, 1.5–2, and 2–3 cm, respectively.[1,40]

Regarding the management of maxillary ameloblastoma involving the orbit, the following strategies can be used alone or in combination with each other[42]:

(i) In tumors not involving orbital fat/soft tissue, a complete resection of the mass may suffice.
(ii) For cases with orbital floor involvement, total maxillectomy is reasonable.
(iii) In cases with orbital soft tissue involvement, orbital exenteration is inevitable.
(iv) Skull base invasion, if occurred, necessitates resection of anterior skull base.

Recurrence after partial resection of the maxillary ameloblastoma results in a tumor with more aggressive behavior with higher mortality rates (33–60%).[1,2] To reduce the recurrence rate, it is wise to perform the MRI and CT for more investigation of tumor extension, preoperatively.[5] In our case, the aforementioned strategies could not be followed based on the patient's choice. This deprived him from an optimal treatment.

Radiotherapy when employed as the first line treatment has a recurrence rate as high as 70%.[2] Even more, there is a study in which all the patients were reported to experience recurrence following the sole radiation therapy.[35] Hence, radiotherapy alone is not wise in the management of ameloblastoma. However, radiotherapy has been shown to be effective in decreasing the tumor size and pain palliation. Hence, radiotherapy can still be placed in our therapeutic arsenal for cases with recurrence, unresectable tumors, and patients who are unable to undergo surgery for any reason.[5,13,35] Possibly, in our case, radiotherapy after orbitotomy could be valuable in controlling or at least delaying the recurrence; however, the patient did not choose it.

The role of chemotherapy in the management of ameloblastoma is an issue of debate. Some authors suggest that ameloblastoma may be sensitive to platinum-based agents. Some[20,43,44] report promising results by this modality for advanced cases while others[5,12,23] maintain that this method is not effective in reducing tumor size or even palliation. In the literature, there are sparse instances of molecular-targeted

therapy that should be further examined in future studies. Kaye et al.[45] reported a patient with multiple recurrent ameloblastoma in the mandible and metastatic ameloblastoma in the lung who harbored a BRAF V600E mutation. The patient was treated with a combination of dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) and achieved a dramatic response after 8 weeks of therapy. Additionally, in another study, reducing the tumor size using vismodegib (SMO inhibitor) was reported.[46]

Prognosis

Generally, prognosis of maxillary ameloblastoma is worse than the mandibular type due to its more recurrence rate, invasion to vital structures, and more advanced stages at the time of diagnosis due to lack of pain or other harbinger symptoms.[23,47] As mentioned earlier, orbital ameloblastoma has an additional tendency to be transformed into the carcinomatous variant. Hence, the prognosis of orbital ameloblastomas in line with tumors involving skull base seems to be the worst.[16,31,36,37,45]

In our review, survival among all cases was 13.47 ± 12.81 years and among different patterns of tumor varied. Among the cases with more than five years of survival (five cases died before 5 years), survival was 16.4 ± 15.1 years in follicular and 18.1 ± 9.9 years in plexiform types, respectively.

We concluded that maxillary ameloblastoma is a locally aggressive neoplasm so that physicians must be alert to the biologic behavior of this tumor to detect any invasion to critical structures such as orbit and cranium. We advocate meticulous patient follow-up with regular clinical examinations and paraclinical work-up (especially MRI) for timely detection of any invasion or recurrence of this tumor. The best must be done to avoid extensions by aggressive removal of maxillary ameloblastoma.

Orbital ameloblastoma causes significant morbidity and mortality. In extensive and longstanding tumors, a multidisciplinary approach is required that may span several specialties i.e. neurosurgery, head and neck surgery/otolaryngology, maxillofacial surgery, ophthalmology, and radiotherapy. This joint effort may take several years to handle the condition to the extent that a recurrence may be detected as late as three decades since the initial diagnosis.

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References

1. Zwahlen RA, Gratz KW. Maxillary ameloblastomas: a review of the literature and of a 15-year database. *J Cranio-Maxillo-Facial Surg*. 2002;30(5):273–279.
2. Reichart PA, Philipsen HP, Sonner S. Ameloblastoma: biological profile of 3677 cases. *Eur J Cancer B Oral Oncol*. 1995;31b(2):86–99.
3. Masthan KM, Anitha N, Krupaa J, Manikkam S. Ameloblastoma. *J Pharm Bioallied Sci*. 2015;7(Suppl 1):S167–S170.
4. Churchill H. Histological differentiation between certain dentigerous cysts and ameloblastoma. *Dent Cosmet*. 1934;76:1173–1178.
5. McClary AC, West RB, McClary AC, et al. Ameloblastoma: a clinical review and trends in management. *Eur Arch Oto-Rhino-Laryngol*. 2016;273(7):1649–1661.
6. Ackermann GL, Altini M, Shear M. The unicystic ameloblastoma: a clinicopathological study of 57 cases. *J Oral Pathol*. 1988;17(9-10):541–546.
7. Appel BN, Verbin RS. Odontogenic tumors. In: *Surgical Pathology of the Head and Neck*. vol. 2. New York, NY: Marcel Dekker; 1985:1332–1343.
8. Gold L. Biologic behavior of ameloblastoma. *Oral Maxillofac Surg Clin North Am*. 1991;3(1):21–27.
9. Chowdhury MOR, Islam S, Chowdhury W, Haque M. Extensive ameloblastoma of the mandible. *TAJ J Teach Assoc*. 2002;15(2):93–95.
10. Taghavi N, Rajabi M, Mehrdad L, Sajjadi SA. 10-year retrospective study on odontogenic tumors in Iran. *Indian J Dent Res*. 2013;24(2):220–224.
11. Milman T, Lee V, LiVolsi V. Maxillary ameloblastoma with orbital involvement: an institutional experience and literature review. *Ophthalmic Plast Reconstr Surg*. 2016;32(6):441–446.
12. Brazis PW, Miller NR, Lee AG, Holliday M. Neuro-ophthalmologic aspects of ameloblastoma. *Skull Base Surg*. 1995;5(4):233.
13. Sato K, Sudo S, Fukuya Y, Sakuma H. Maxillary ameloblastoma with intracranial invasion—case report—. *Neurol Med-Chir*. 1994;34(10):704–707.
14. Kyriazis AP, Karkazis GC, Kyriazis AA. Maxillary ameloblastoma with intracerebral extension: report of a case. *Oral Surg Oral Med Oral Pathol*. 1971;32(4):582–587.
15. O'brien C, Leinfelder P. Unilateral exophthalmos: etiologic and diagnostic studies in eighty-two consecutive cases. *Trans Am Ophthalmol Soc*. 1934;32:324.
16. Linnert D. [Ophthalmological findings after surgical treatment of orbital tumors]. *Klin Monbl Augenheilkd*. 1970;156(4):507–516.
17. Spaeth E. Information learned from fifty years of orbital exenteration. *Trans Ophthalmol Soc U K*. 1971;91:611.
18. Shaw H, Katsikas D. Ameloblastoma of the maxilla A clinical study with four cases. *J Laryngol Otol*. 1973;87(09):873–884.
19. Tsaknis P, Nelson J. The maxillary ameloblastoma: an analysis of 24 cases. *J Oral Surg*. 1980;38(5):336–342.
20. Daramola J, Abioye A, Ajagbe H, Aghadiuno P. Maxillary malignant ameloblastoma with intraorbital extension: report of case. *J Oral Surg Am Dent Assoc 1965*. 1980;38(3):203–206.
21. Komisar A. Plexiform ameloblastoma of the maxilla with extension to the skull base. *Head Neck Surg*. 1984;7(2):172–175.
22. Weiss JS, Bressler SB, Jacobs EF, Shapiro J, Weber A, Albert DM. Maxillary ameloblastoma with orbital invasion: a clinicopathologic study. *Ophthalmology*. 1985;92(5):710–713.
23. Bredenkamp JK, Zimmerman MC, Mickel RA. Maxillary ameloblastoma: a potentially lethal neoplasm. *Arch Otolaryngol Head Neck Surg*. 1989;115(1):99–104.
24. Moster Mark L, Harwick R, Chan G, Scimeca G. A progressive cavernous sinus syndrome in a young woman. In: *Presented at the 23rd Annual Frank B Walsh Society Metting, Salt Lake City, Utah*. 1991.
25. Henderson J, Campbell R, Farrow G, Garrity J. Cysts. In: *Orbital Tumors*. vol. 3. 1994:53–88.
26. Hayashi N, Iwata J, Masaoka N, Ueno H, Ohtsuki Y, Moriki T. Ameloblastoma of the mandible metastasizing to the orbit with malignant transformation. *Virchows Arch*. 1997;430(6):501–507.
27. Leibovitch I, Schwarcz RM, Modjtahedi S, Selva D, Goldberg RA. Orbital invasion by recurrent maxillary ameloblastoma. *Ophthalmology*. 2006;113(7):1227–1230.
28. Herwig M, Fischer H, Moore C, et al. Orbitale infiltration durch ein ameloblastom der maxilla. *Der Ophthalmol*. 2013;110(3):251–254.
29. Faras F, Abo-Alhassan F, Israel Y, Hersant B, Meningaud JP. Multirecurrent invasive ameloblastoma: a surgical challenge. *Int J Surg Case Rep*. 2017;30:43–45.

30. Morgan PR. Odontogenic tumors: a review. *Periodontol 2000*. 2011;57(1): 160–176.
31. Oliveira LR, Matos F, Dominguete R, Zorgetto A, Ribeiro A. Ameloblastoma: report of two cases and a brief literature review. *Int J Odontostomat*. 2011;5(3):293–299.
32. Mosadomi A. Odontogenic tumors in an African population. Analysis of twenty-nine cases seen over a 5-year period. *Oral Surg Oral Med Oral Pathol*. 1975;40(4):502–521.
33. Lu Y, Xuan M, Takata T, et al. Odontogenic tumors. A demographic study of 759 cases in a Chinese population. *Oral Surg Oral Med Oral Pathol, Oral Radiol, Endod*. 1998;86(6):707–714.
34. Anand SV, Davey WW, Cohen B. Tumours of the jaw in West Africa. A review of 256 patients. *Br J Surg*. 1967;54(11):901–917.
35. Sehdev M, Huvos A, Strong E, Gerold F, Willis G. Ameloblastoma of maxilla and mandible. *Cancer*. 1974;33(2):324–333.
36. Kessler HP. Intraosseous ameloblastoma. *Oral Maxillofac Surg Clin North Am*. 2004;16(3):309–322.
37. Brown NA, Betz BL. Ameloblastoma: a review of recent molecular pathogenetic discoveries. *Biomarkers Cancer*. 2015;7(Suppl 2):19–24.
38. Dunfee BL, Sakai O, Pistey R, Gohel A. Radiologic and Pathologic Characteristics Of benign and malignant lesions of the mandible 1. *Radiographics*. 2006;26(6):1751–1768.
39. Underhill T, Katz J, Pope Jr T, Dunlap C. Radiologic findings of diseases involving the maxilla and mandible. *AJR Am J Roentgenol*. 1992;159(2): 345–350.
40. Becelli R, Carboni A, Cerulli G, Perugini M, Iannetti G. Mandibular ameloblastoma: analysis of surgical treatment carried out in 60 patients between 1977 and 1998. *J Craniofacial Surg*. 2002;13(3): 395–400.
41. Cohen MA, Hertzanu Y, Mendelsohn DB. Computed tomography in the diagnosis and treatment of mandibular ameloblastoma: report of cases. *J Oral Maxillofac Surg*. 1985;43(10):796–800.
42. Jackson I, Callan P, Forté RA. An anatomical classification of maxillary ameloblastoma as an aid to surgical treatment. *J Cranio-Maxillofac Surg*. 1996;24(4):230–236.
43. Amzerin M, Fadoukhair Z, Belbaraka R, et al. Metastatic ameloblastoma responding to combination chemotherapy: case report and review of the literature. *J Med Case Rep*. 2011;5:491.
44. Ciment LM, Ciment AJ. Malignant ameloblastoma metastatic to the lungs 29 years after primary resection: a case report. *CHEST J*. 2002;121(4): 1359–1361.
45. Kaye FJ, Ivey AM, Drane WE, Mendenhall WM, Allan RW. Clinical and radiographic response with combined BRAF-targeted therapy in stage 4 ameloblastoma. *J Natl Cancer Inst*. 2015;107(1):378.
46. Ally MS, Tang JY, Joseph T, et al. The use of vismodegib to shrink keratocystic odontogenic tumors in patients with basal cell nevus syndrome. *JAMA Dermatol*. 2014;150(5):542–545.
47. Reija MG, Izquierdo M, Rueda JB, Cantera MG, Hernández AV. Ameloblastomas maxillaries: a propósito de dos casos clínicos. *Acta otorrinolaringol Espanola*. 2001;52(3):261–265.