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Case Presentation

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Recurrent Ameloblastoma-Associated Hypercalcemia: Report of Two Non-Metastatic Cases

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Abstract

Ameloblastoma is one of the most common benign odontogenic tumor, characterized by slow but destructive growing and a very high tendency to relapse. Malignant transformations of ameloblastoma are rarely seen, accounting for less than 1% of the cases. Hypercalcemia is the most common metabolic complication of malignancy. It is an unusual symptom associated with ameloblastoma. Hypercalcemia in ameloblastoma usually causes a more aggressive and recurrent type of tumour that may lead to an increased tendency to metastasis. Hypercalcemia in ameloblastoma is a strong predictor for malignant transformation and lung metastasis Its mechanism of onset is not exactly clarified. The primary cause of hypercalcaemia is *local osteolytic hypercalcaemia* (LOH). The second possible mechanism is *humoral hypercalcemia of malignancy* (HHM), while excessive production of parathyroid hormone-like protein (PTHrP) in ameloblastomas has been previously reported. Hypercalcemia therapy depends upon its etiology. In patients with hypercalcemia of malignancy, progressive hypercalcemia will inevitably accompany tumor progression, and therefore, the underlying disease causing the hypercalcemia should be treated, if at all possible. We report the cases of a 47-year-old man with mandibular ameloblastoma and concomitant clinically silent hypercalcemia, and of a 65-years old female patient with ameloblastoma in the mandible with silent hypercalcemia. The patients underwent tumor excision and lower jaw

reconstruction, which totally corrected the hypercalcemia.

Keywords: Ameloblastoma; Ameloblastic carcinoma; Hypercalcemia

Introduction

Ameloblastoma is the second most prevalent benign odontogenic tumor of the mandible with a high recurrence rate (50-70%), which is further complicated by patients' psychological status affecting their coping behaviors and timely diagnosis [1,2]. Ameloblastomas with repeated recurrence or those left untreated until growing significantly, may transform into ameloblastic carcinomas, which have been reported to induce hypercalcemia in some cases [3-5]. Hypercalcemia is a very common metabolic disorder of malignant tumors; therefore, its incidence with ameloblastoma is a strong predictor for malignant transformation and lung metastasis [6]. This article aims to describe the history, clinical and histological findings, surgical, and medical management of two cases of recurrent locally invasive ameloblastoma associated with hypercalcemia. On preoperative examination, calcium level was remarkably above the physiological range; therefore, the access to surgery required stabilization of serum calcium values. Postoperative Computed Tomography (CT) examination yielded no evidence of oncologic recurrence or lung metastasis.

Ameloblastoma

Ameloblastoma is one of the most common benign odontogenic tumors [7], characterized by slow, but invasive and destructive growing and it presents a high risk of recurrence and a low tendency of metastases [8,9]. Ameloblastomas occur mainly as hard lesions. They are mostly asymptomatic, but may be present due to slow growing, pain, paresthesia and edematous infiltration of the surrounding tissue. Although it is considered the most common odontogenic epithelial tumor, it accounts for 1% of all oral tumors. Clinical studies do not show a predilection for sex, race, or age. Approximately 80% of ameloblastomas occur near the angle of the mandible in the area of the third molar, the minority originates in the maxilla (20%) [10-12]. This localization in maxilla is characterized by more aggressive growth, destruction of the maxillary sinus, the base of the orbit, and possible growth to the skull base. The denser cortical layer of the mandibular bone prevents aggressive growth compared to the maxilla. Ameloblastoma is of ectodermal origin and arises from ameloblasts, which are part of the odontogenic epithelium and are responsible for the production of enamel. Histopathologically, according to WHO *(World Health Organization, 2005*), ameloblastoma is divided into 4 types:

- solid/multicystic (86%) - histopathological subtypes are follicular (acanthomatous, granular, desmoplastic, basal cell type) and plexiform types
- extraosseous/peripheral (1%)
- desmoplastic
- unicystic (13%) – histopathological subtypes are luminal and mural [13].

Therapy

The recurrence of ameloblastoma is common and unpredictable [14]. The recurrence rate for wide resection is 3.6%, for enucleation is 30.5%, and for enucleation followed by use of Carnoy's solution is 16% [12]. From this perspective, wide resection of the involved jaw is therefore recommended [15]. Risk predictors of recurrence are the size of the primary tumor being larger than 6 cm, the invasion to soft tissues or adjacent anatomical structures regardless of the surgical method [14]. Malignant transformations of ameloblastoma are rarely seen,

accounting for less than 1% of the cases. Malignant ameloblastoma may arise *de novo* or from transformation of pre-existing ameloblastoma [12]. Laboratory signs of malignant transformation is hypercalcemia and also leukocytosis, and elevation of serum Squamous Cell Carcinoma (SCC) antigen and Carcino-Embryonic Antigen (CEA) levels [8].

Hypercalcemia

Hypercalcemia is the most common metabolic complication of malignancy [16]. Although it is often reported in association with other malignancies (breast, lung, renal, bladder, lymphoma, ovarian, myeloma or other hematological malignancies), it is rarely associated with ameloblastoma. Hypercalcemia in ameloblastoma is a strong predictor for malignant transformation and lung metastasis [17]. The mechanisms of hypercalcemia related to ameloblastoma is still not well understood due to the limited number of cases with the occurrence of hypercalcemia in ameloblastomas [17]. The primary cause is bone resorption - *Local Osteolytic Hypercalcemia (LOH).* The second possible mechanism is humoral hypercalcemia - *Humoral Hypercalcemia of Malignancy (HHM),* while excessive production of Parathyroid Hormone-like Protein (PTHrP) in ameloblastomas has been previously reported [16].

Hypercalcemia is defined as a high level of serum calcium (Ca^{2+}) above the normal level, which is in the range of 2.15 - 2.65 mmol/l (8.8-10.7 mg/dl, 4.3-5.2 mEq/l) [18,19] A concentration above 3.75 mmol/l is considered critical and life-threatening [20]. Calcium is one of the most important and common minerals in the body. It is a major component of the mineralized tissues comprising more than 99% of total body calcium (*irreplaceable pool*) [21,22]. Only 0.5% in the body represents an exchangeable pool, of which approximately half is calcium located in serum bound to proteins, primarily albumin. Calcium participates in the regulation of various physiological processes, such as normal growth and development, intracellular processes, protein formation, muscle fiber contraction, and nerve impulse transmission. It is part of blood coagulation, and it participates in the development of teeth. Only free calcium cations are biologically active.

Clinical Manifestations of Hypercalcemia

Hypercalcemia may be associated with a spectrum of clinical manifestations (fatigue, exhaustion, apathy, muscle weakness, bone pain with pathological fractures even with a minimal injury, arhythmia, vomiting, cognitive dysfunction, coma), depending upon the degree of hypercalcemia and the rate of onset of the elevation in the serum calcium concentration. In addition, there is individual variation in the manifestation of symptoms [20].

Treatment of Hypercalcemia

Hypercalcemia therapy depends upon its etiology. In patients with hypercalcemia of malignancy, progressive hypercalcemia will inevitably accompany tumor progression, and therefore, the underlying disease causing the hypercalcemia should be treated, if at all possible. Adequate hydration (at least six to eight glasses of water per day) is recommended to minimize the risk of nephrolithiasis [20]. In the first line, it is mandatory to treat the hypercalcemia itself and then the etiology. Asymptomatic or mildly symptomatic hypercalcemia (< 3.5 mmol/l) requires sufficient hydration (perhaps intravenously in a volume of 3-6 liters) and elimination of drugs that increase the calcium level (thiazide diuretics, antacids, calcium supplements) [18]. Patients with hypercalcemia up

to 3.5 mmol/l require more aggressive therapy [20]. Initial therapy of severe hypercalcemia includes the simultaneous administration of *intravenous isotonic saline* (initial rate of 200 to 300 ml/hour), subcutaneous *calcitonin* (the initial dose is 4 units/kg), and the use of *bisphosphonate medication*. In the absence of renal failure or heart failure, loop diuretic therapy to directly increase calcium excretion is not recommended. If hypercalcemia does not respond to the therapy, dialysis is indicated. It is also indicated in patients with severe malignancy-associated hypercalcemia and renal insufficiency or heart failure, in whom hydration cannot be safely administered [19].

Case Presentation

Case 1

A 48-years old male patient was referred to our department presenting with tumorous formation on the left side of his face that started to grow six years before. During these years, the patient did not lose weight and continued to eat without restrictions. He reported occasional pain, rather in the evening before bedtime, relieved by Non-Steroidal Anti-Inflammatory Drugs (NSAID). The patient history revealed an edematous formation on the left side of his face started 12 years before, with suspicious mandibular cysts. In the following 2 years, the patient underwent cystectomy, mandibular resection, and reconstruction with splint, and since that time, he did not seek any medical care. On physical examination, a significant facial asymmetry was observed with tumor resistance of stiff-elastic consistency starting 2.5 cm below the infraorbital margin and deforming the middle and lower thirds of the face. Submandibular fistulation was detected with an outlet of serous fluid and local erythema around the fistulation. The skin on the other surface of the lesion was intact and functions of the fifth and seventh nerves were preserved. Intraoral examination revealed an exulcerated lesion ranging from the maxilla region of the 26 extending caudally to the mandible and the molar region from the vestibular and lingual areas to the regon of the 33, sublingually to oropharynx left. Histological investigation concluded a peripheral type ameloblastoma. The patient was admitted to the internal department preoperatively due to increased calcium level (3.48) that contraindicated the procedure under general anesthesia. He was treated intensively with intravenous therapy of furosemide, prednisone, and kaldyum tablets, in addition to forced diuresis for ten days until the calcium level reached an acceptable level (3.0). Two surgical teams worked simultaneously, where two surgeons raised a microvascular fibular flap from the lower right leg, and three surgeons resected the tumorous lesion that resulted in a 14*11*7.5 cm segment of the mandible with lower teeth and adjacent soft tissues. However, all of the margin cuts were tumor free, resection was extended to infratemporal fossa and foramen ovale. On the morning following surgery, calcium level dropped rapidly to 2.06 and during the postoperative care (16 days) it reached 1.67. After stabilization, the patient was placed under home treatment for 20 days while calcium level was 2.01. Three months later, Positron Emission Tomography – Computed Tomography (PET/CT) scan was conducted to exclude metastatic bearings anywhere in the body. Heretofore, the patient is still monitored while being prepared for prosthetic rehabilitation **(Figure 1-3).**

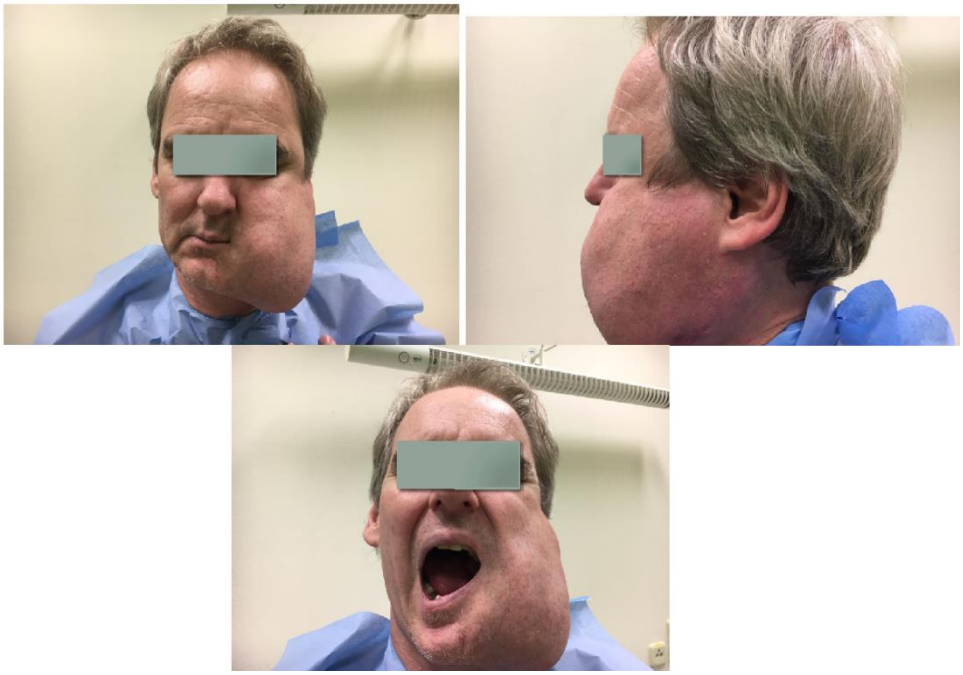

Figure 1: Ameloblastoma of the left mandible.

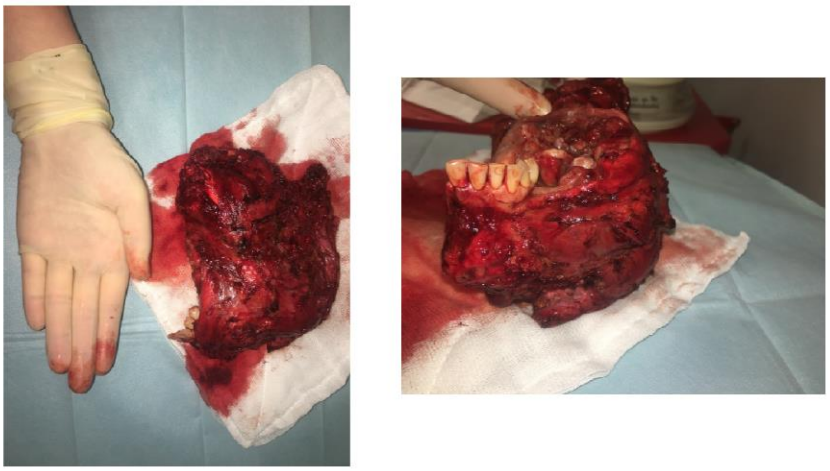

Figure 2: Left mandibular mass after resection.

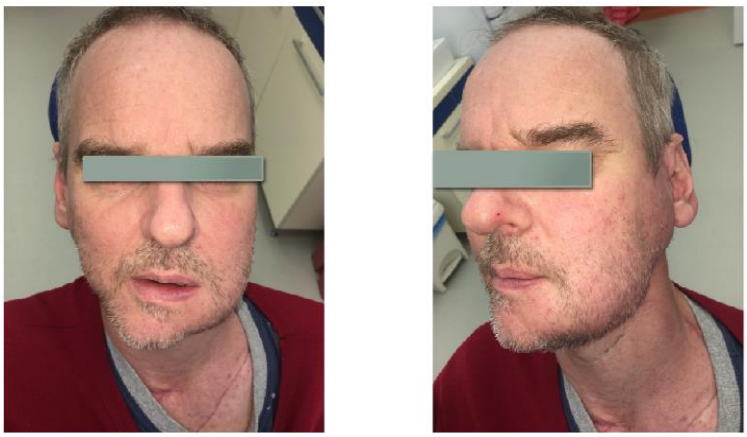

Figure 3: Post-operative 6-week follow-up after resection.

Case 2

A 65-years old female patient was referred to our department by her dentist presenting with large tumorous formation in the left side of her face. On checking the patient's records, it was noticed that her first dental visit occurred when she was 19-years old due to mandibular cystic formation that was filled with pelvic bone augmentation. Three years later, the patient presented an alleged cystic bearing required mandibular resection and osteoplasty of the rib. Twenty-five and thirty-five years later, the patient underwent histologic examination that presented a diagnosis of ameloblastoma; however, the patient had embolectomy until 2016 without effect. Psychiatric findings dominated the long-term treatment of claustrophobia and anxiety, in addition to diabetes mellitus type 2, arthritis urica, and arterial hypertension. Physical examination revealed multilobular tumor interfering intraorally and extending from preauricular region until submandibular. The skin on the surface of the tumor was purple with tiny tumors in the form of hemangiomas. The opening of the mouth was limited by a tumorous process that deformed the entire mucous area of the left cheek and oppressed the tongue. For psychiatric diagnoses, the patient underwent preoperative treatment for Neurol and Escitil. Elevated potassium levels (5.54) and calcium levels (3.34) above the physiologic range were observed preoperatively and reduced by diuretic therapy. After adjusting the mineralogram, we performed surgery in the schope of bronchoscopis intubation, tracheostomy, tumor resection-hemimandibulectomy with reconstruction using fibula free flap. Perioperatively, the patient required hemosubstition with intermitent need for sympathomimetic blood circulation support with dobutamine. Histological conclusion of the tumor with tumor free margin was concluded as ameloblastoma granular cell type. Postoperatively, the calcium level dropped to 1.99 mmol/l.

Discussion

Although hypercalcemia is the most common metabolic complication of malignancy, it is rarely associated with ameloblastoma. Hypercalcaemia in ameloblastoma is a strong predictor for malignant transformation and lung metastasis. It usually causes a more aggressive and recurrent type of tumour that may lead to an increased tendency to future metastasis. Due to the high rate of recurrence of ameloblastoma, long-term follow up is recommended for more than 10 years. Risk predictors of recurrence are also the size of the primary tumor larger than 6 cm, the invasion to soft

tissues and anatomical structures, regardless of the surgical method.

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References

1. Dissanayake RKG, Jayasooriya PR, Siriwardena DJL, Tilakaratne WM. Review of metastasizing (malignant) ameloblastoma (METAM): Pattern of metastasis and treatment. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2011;111(6):734-41.
2. Zabora J, BrintzenhofeSzoc K, Curbow B, Hooker C, Piantadosi S. The prevalence of psychological distress by cancer site. Psychooncology. 2001;10(1):19-28.
3. Cox DP, Muller S, Carlson GW, Murray D. Ameloblastic carcinoma ex ameloblastoma of the mandible with malignancy-associated hypercalcemia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2000;90(6):716-22.
4. Ghiam AF, Al Zahrani A, Feld R. A case of recurrent metastatic ameloblastoma and hypercalcaemia successfully treated with carboplatin and paclitaxel: Long survival and prolonged stable disease. Ecancermedicalscience. 2013:7:323.
5. Harada K, Suda S, Kayano T, Nagura H, Enomoto S. Ameloblastoma with metastasis to the lung and associated hypercalcemia. J Oral Maxillofac Surg. 1989;47(10):1083-7.
6. Lo TEN, Villafuerte CV, Acampado LT. Overwhelming hypercalcaemia in mandibular ameloblastoma. BMJ Case Rep. 2014;2014:bcr2014205491.
7. Guha A, Schalek P, Chovanec M. Parciální maxilektomie pro ameloblastom horní čelisti s postižením infratemporální fossy: kombinovaný endonazální a transorální přístup. Conference: 80. kongres České společnosti otorinolaryngologie a chirurgie hlavy a krku ČLS JEP. 2018.
8. Ota Y, Aoki T, Otsuru M, Hirabayashi K, Nakamura N, Tsukinoki K. Huge Ameloblastoma Associated With Hypercalcemia, Leukocytosis, and Elevated Tumor Markers via Production of Parathyroid Hormone–Related Protein and Granulocyte Colony-Stimulating Factor. J Oral Maxillofac Surg. 2012;70(6):1380-5.
9. Jayaraj G, Sherlin HJ, Ramani P, Premkumar P, Natesan A, Ramasubramanian A, et al. Metastasizing Ameloblastoma – A perennial pathological enigma? Report of a case and review of literature. J Craniomaxillofac Surg. 2014;42(6):772-9.
10. 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):501-7.
11. Karakida K, Aoki T, Sakamoto H, Takahashi M, Akamatsu T, Ogura G, et al. Ameloblastic carcinoma, secondary type: a case report. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010;110(6):e33-7.
12. Hariram, Mohammad SS, Malkunje LR, Singh N, Das S, Mehta G. Ameloblastoma of the anterior mandible. Natl J Maxillofac Surg. 2014;5(1):47-50.

13. Hertog D, Bloemena E, Aartman IHA, Van-der-Waal I. Histopathology of ameloblastoma of the jaws; some critical observations based on a 40 years single institution experience. Med Oral Patol Oral Cir Bucal. 2012;17(1):e76-82.
14. Yang R, Liu Z, Gokavarapu S, Peng C, Ji T, Cao W. Recurrence and cancerization of ameloblastoma: multivariate analysis of 87 recurrent craniofacial ameloblastoma to assess risk factors associated with early recurrence and secondary ameloblastic carcinoma. Chin J Cancer Res. 2017;29(3):189-95.
15. Dandriyal R, Gupta A, Pant S, Baweja HH. Surgical management of ameloblastoma: Conservative or radical approach. Natl J Maxillofac Surg. 2011;2(1):22-7.
16. Cox DP, Muller S, Carlson GW, Murray D. Ameloblastic carcinoma ex ameloblastoma of the mandible with malignancy-associated hypercalcemia. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2000;90(6):716-22.
17. Lo TE, Villafuerte CV 3rd, Acampado LT. Overwhelming hypercalcaemia in mandibular ameloblastoma., BMJ Case Rep. 2014;2014:bcr2014205491.
18. Broulík P. Hyperkalcemie: na co je třeba myslet a jaká vyšetření provést?. Interní Med. 2011;13(7):314-317.
19. Mayo Clinic Home Page. Hypercalcemia.
20. Shane E, Berenson JR. Treatment of hypercalcemia. UpToDate. 2023.
21. Shane E. Clinical manifestations of hypercalcemia. UpToDate. 2023.
22. Ferreira TSH, Pimentel IMF, Albuquerque LAF, Gondim JA. Pure endoscopic transsphenoidal treatment of skull base ameloblastoma with intracranial extension: Case report and literature review. Surg Neurol Int. 2020:11:228.

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