CASE REPORT

Overwhelming hypercalcaemia in mandibular ameloblastoma

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SUMMARY

Ameloblastoma is considered to be a benign odontogenic tumour of epithelial in origin that is slow growing but recurrent and invasive in nature. Some of its features have been sources of debate among experts regarding its benign or malignant character. We report a case of a 20-year-old Filipino woman with right mandibular ameloblastoma presenting with overwhelming hypercalcaemia. Work ups for hypercalcaemia eventually revealed tumoral hypercalcaemia, which was initially controlled with intravenous bisphosphonate. The patient eventually underwent tumour excision and mandibular reconstruction, which totally corrected hypercalcaemia. This case will highlight the rare association of hypercalcaemia among patients with ameloblastoma.

BACKGROUND

Mandibular swelling can be attributed to a lot of causes and can be divided into odontogenic and non-odontogenic in origin.¹ Of all the causes of mandibular swelling, odontogenic tumours accounts for 9% and included under this group is ameloblastoma which accounts for 1% of tumours.² It is the second most common odontogenic tumour that mostly involves the mandible and maxilla.³ It is an odontogenic tumour of the jaws, arising from dental embryonic remnants possibly from the epithelial lining of an odontogenic cyst; dental lamina or enamel organ; stratified squamous epithelium of the oral cavity; or displaced epithelial remnants.⁴ The WHO defines it as a locally invasive polymorphic neoplasia that often has a follicular or plexiform pattern in a fibrous stroma. Its behaviour has been described as being benign but locally aggressive.⁵

It is a slow growing locally invasive epithelial tumour with a high recurrence rate (50%–72%) and rare metastasis (<2%).⁶ Histopathologically, metastasising ameloblastoma shows no specific features different from non-metastatic ameloblastoma, which makes it impossible to predict its clinical behaviour.⁷ Metastasis usually follows multiple recurrences and frequently occurs in the lungs (≥75%) and cervical lymph nodes, usually many years after the primary tumour.⁸ The question of malignancy in ameloblastoma has been the subject of considerable discussion and controversy for many years. The ability of some form of ameloblastoma to metastasise provides more confusion with regard to its malignant potential since these lesions might show unusually benign histological features.⁹

Figure 1 Orthopantomogram radiograph showing a unilocular radioluscent area with displacement of teeth and significant resorption of the right mandibular ramus.

Paraneoplastic endocrine syndromes generally result from tumour production of hormones or peptides that lead to metabolic derangements. Hypercalcaemia is the most common metabolic complication of malignancy. It is estimated to affect up to 8% of patients with cancer and generally conveys a poor prognosis.¹⁰ Hypercalcaemia in malignancy can be divided into two syndromes, humoral hypercalcaemia of malignancy and local osteolytic hypercalcaemia, based on whether a circulating hormone or local paracrine factors mediate accelerated bone resorption.¹¹ Although hypercalcaemia of malignancy is often reported in association with other malignancies such as breast, lung, renal, bladder, lymphoma, ovarian, myeloma or other hematological malignancies, it is rarely associated with ameloblastoma.¹²

This paper will describe and highlight a case of mandibular ameloblastoma in a young Filipino woman presenting with a gradually enlarging and disfiguring mandibular mass with concomitant hypercalcaemia of malignancy.

Figure 2 Initial biopsy of the right mandibular mass revealing ameloblastoma.

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Figure 3 Right mandibular ameloblastoma resulting in significant disfigurement and alteration of mandibular mobility and adjacent structures. (A) Lateral view and (B) anterior view.

CASE PRESENTATION

Our case begins with a 20-year-old Filipino woman presenting with a 10-month history of recurrent right cheek swelling associated with pain. The patient had several dental consults initially presumed to have swollen unerupted tooth and was given antibiotics (amoxicillin) which partially relieved the symptoms. Persistence of the right buccal swelling now associated with a palpable right mandibular mass prompted consult with an otorhinolaryngologist. Initial orthopantomogram performed revealed a well-defined sclerotic, unilocular radioluscent area with tooth extending to the ramus of the mandible (figure 1). Diagnosis of a possible odontogenic tumour was made and eventually confirmed by a tissue biopsy revealing the diagnosis of ameloblastoma (figure 2). The patient was initially offered surgery but was lost to follow-up.

In the interim, the patient noted gradual enlargement of the right mandibular tumour leading to facial disfigurement,

malocclusion, loosening of the right mandibular teeth, occasional oral bleeding and eventually dysphagia to solid food due to hypopharyngeal compression by the enlarging tumour. She also had several hospital admissions for recurrent oral bleeding, infection (abscess formation) and dehydration from excessive salivation with poor oral intake. And also developed gradual weight loss leading to severe malnutrition due to inability to take solid food. The patient was eventually admitted in our institution when she presented with a 3-day history of dizziness, abdominal pain, nausea and vomiting leading to lethargy. Presence of halitosis and foul smelling oral discharge were also noted on admission.

Physical examination revealed a generally cachectic and malnourished (BMI=14.8) patient with a large (12×15 cm) swollen right disfiguring mandibular mass with fungating lesion at the buccal cavity. Tongue was deviated to the left and slightly protruded due to the large mass leading to excessive salivation

Table 1 Biochemical tests conducted during hospitalisation

Diagnostic test	Normal values	Result	Interpretation
Complete blood count	WCC→4.5–11.0×10 ⁹ /L Haemoglobin→120–180 g/L Platelet→150–450×10 ⁹ /L	20.69 145 313	Leukocytosis→on-going infection from an infected mandibular tumour
Urinalysis	Cast and crystals (-)	Negative	Unremarkable
Arterial blood gas	pH→7.40 HCO ₃ →22–26 pCO ₂ →45	7.539 19.3 22.5	Respiratory alkalosis with metabolic acidosis→on-going sepsis
Random blood sugar	74–118 mg/dL	66	Mild hypoglycaemia→poor oral intake
Serum sodium	136–144 mmol/L	124	Hyponatremia→poor intake and excessive salivation
Serum potassium	3.6–5.1 mmol/L	2.5	Hypokalemia→poor intake and excessive salivation
Serum calcium	2.23–2.58 mmol/L	4.4	Hypercalcaemia→hypercalcaemia of malignancy
Serum magnesium	0.70–1.0 mmol/L	0.72	Normal
Serum phosphorus	0.81–1.49 mmol/L	0.53	Hypophosphataemia
Albumin	35–48 g/L	25	Hypoalbuminaemia→malnutrition from poor oral intake
Blood urea nitrogen	2.9–9.3 mmol/L	4.3	Normal
Creatinine	0.44–1.03 mg/dL	0.93	Normal Renal Function
Alkaline phosphatase	38–126 IU/L	270	Elevated→High bone turnover
Intact PTH	10–65 pg/mL	0.6	Low→hypercalcaemia of malignancy
Serum vitamin D	20–79 ng/mL	34	Normal

PTH, parathyroid hormone; WCC, white cell count.

Figure 4 Head and neck CT scan demonstrating bony destruction and extensive soft tissue involvement by the unilocular solid right mandibular tumour. (A) Coronal view and (B) transverse view.

(figure 3A, B). Oral examination revealed multiple dental caries mostly involving the right mandibular teeth and a right parapharyngeal bulge occluding the hypopharynx. Vocal cords were fully mobile and unremarkable. Nasal septum and turbinates were also unremarkable. There were neither neck masses nor lymphadenopathies noted. Other systemic physical findings were all unremarkable.

INVESTIGATIONS

Initial biochemical work ups revealed leukocytosis, multiple electrolyte imbalance, hypoalbuminaemia, hypoglycaemia and normal renal function. An incidental severe hypercalcaemia despite poor intake and hypophosphataemia were noted hence referral to our service for management and work up of hypercalcaemia was made (table 1). Specific work ups for the cause of hypercalcaemia revealed a normal serum vitamin D (32 mg/mL; normal value (NV)=20–79 ng/mL) and a low intact parathyroid hormone (0.6 pg/mL; NV=10–65 pg/mL) in a patient presenting with an obvious tumour suggested the possibility of hypercalcaemia of malignancy.

Initial radiological work up using neck ultrasound identified a mass at the right facial and upper neck region characterised as a heterogeneous solid tumour with internal vascularity and measuring at least 13×10×6 cm in size without involving the right parotid and submandibular glands. The thyroid gland and cervical lymph nodes were all unremarkable. Head and neck CT

scan demonstrated bony destruction and extensive soft tissue involvement by the well-defined calcified unilocular solid right mandibular tumour (figure 4A, B). Three-dimensional reconstruction of the skull showed significant bone resorption of the right mandibular ramus leading to its near total disappearance (figure 5A, B). Metastatic screening using routine chest X-ray and abdominal ultrasound did not show any lung or liver metastases. Repeat biopsy of the mass confirmed the diagnosis of ameloblastoma in this case.

DIFFERENTIAL DIAGNOSIS

When a patient with a known tumour presents with hypercalcaemia, there are a lot of differentials that should be considered before assuming hypercalcaemia to be related to the tumour. Drugs (thiazide diuretics), calcium intake, vitamin D supplementation and other known renal or hepatic comorbidities that might contribute and cause hypercalcaemia should be first ruled out. Causes of hypercalcaemia can be grouped into five main categories: hyperparathyroidism, hypercalcaemia of malignancy, vitamin D-related hypercalcaemia, renal failure-related hypercalcaemia and high bone turnover (immobilisation, vitamin A intoxication, hyperthyroidism). Hyperparathyroidism usually presents with significantly elevated intact parathyroid hormone on a background of a slightly elevated calcium level. Vitamin D-related hypercalcaemia would present with hypercalcaemia and

Figure 5 Three-dimensional reconstruction of the skull showing significant bone resorption of the right mandibular ramus. (A) Right lateral view and (B) left lateral view.

Figure 6 Preoperative and postoperative calcium trends showing complete resolution of hypercalcaemia after surgical tumour removal.

Table 2 Biochemical comparison before and after surgical tumour excision

Parameter	Normal values	Preoperative result	Postoperative result
Serum calcium	2.23–2.58 mmol/L	4.4	2.35
Serum phosphorus	0.81–1.49 mmol/L	0.53	1.12
Intact PTH	10–65 pg/mL	0.6	27.82
Alkaline phosphatase	38–126 IU/L	270	108

PTH, parathyroid hormone.

hyperphosphataemia with a history of an elevated vitamin D levels. Renal failure hypercalcaemia is seen among patients with chronic kidney disease with poor renal function and is

Figure 7 Gross appearance of the right mandibular mass after surgical excision.

usually associated with hyperphosphataemia. Our patient presented with hypercalcaemia, hypophosphataemia, normal renal function, normal vitamin D levels and a suppressed intact parathyroid hormone level. All of these findings plus the presence of a tumour points out to the diagnosis of tumour-related hypercalcaemia. Resolution of hypercalcaemia after removal of the tumour further strengthened the diagnosis of tumour-related hypercalcaemia in this case.

TREATMENT

On admission, the patient was initially stabilised with intravenous glucose-containing fluids and several electrolytes which corrected the patient's dehydration, hypoglycaemia and multiple electrolyte imbalances. The patient was inserted with a nasogastric tube

Figure 8 Final histological biopsy report confirming ameloblastoma within an intact capsule without malignant features (A and B) based on presence of stellate reticular matrix (C) and reverse polarisation among epithelial cells (D).

Figure 9 The patient after tumour excision.

and started on up-building diet to correct malnutrition. She was also loaded with broad-spectrum antibiotics (piperacillin-tazobactam 4.5 g intravenously every 8 h) to cover for the ongoing buccal infection brought about by the tumour. With those several supportive measures mentioned, the patient clinically improved leading to better sense of well-being, strength and appetite. Hypercalcaemia was initially managed with hydration and use of diuretics until a pamidronate infusion was needed to adequately lower the calcium level prior to the proposed operation. The patient eventually underwent wide tumour excision and right mandibulectomy which effectively resulted in normalisation of the serum calcium, phosphate, alkaline phosphatase and intact parathyroid hormone levels (figure 6 and table 2).

OUTCOME AND FOLLOW-UP

A 12×12×8 cm, irregular, firm, tan-brown mass with five loosely attached teeth weighing 1340 g was excised and sent to pathology for further diagnosis (figure 7). Histological assessment of the tumour did not show any malignant potential or features as evidenced by an intact capsule and well-

differentiated cellular structures (figure 8A, B). Typical findings of reverse cellular polarisation embedded on a stellate reticular matrix were seen on final histological report further confirming the diagnosis of ameloblastoma (figure 8C, D). The patient then had subsequent follow-ups on out-patient setting without recurrence of hypercalcaemia (figure 9). She was then optimised preoperatively and eventually underwent mandibular reconstruction after 2 months where part of her fibula was taken and made as a bridge of the mandibular ramus leading to better mastication. After 2 months of rehabilitation, the patient now is able to chew well and function normally as an individual.

DISCUSSION

With the benign nature of ameloblastoma, it is surprisingly rare for this type of tumour to present with hypercalcaemia. Indeed, in a review of literature, only six cases of ameloblastoma presented with concomitant hypercalcaemia. All reported cases were highly aggressive and recurrent forms of ameloblastoma with malignant transformation in five cases. Majority had the propensity to metastasise occurring from 1 to 45 years after initial tumour resection (table 3).^{3 12–16}

There are four principal mechanisms of tumour-related hypercalcaemia. Secretion of parathyroid hormone-related protein (PTHrP) by tumour cells—known as humoral hypercalcaemia of malignancy—accounts for majority (80%) of cases and occurs most commonly with squamous cell tumours. The remaining 20% of cases arise directly from osteolytic activity at sites of skeletal metastases where breast cancer, multiple myeloma and lymphomas are seen. On rare occasions, hypercalcaemia may result from tumour secretion of vitamin D commonly seen among lymphomas or from ectopic tumour secretion of parathyroid hormone.¹⁷

Mechanisms of hypercalcaemia related to ameloblastoma are still poorly understood due to limited data. Local osteolytic hypercalcaemia caused by osteoclastic bone resorption in proximity to skeletal tumour deposit appears to be an obvious cause since most of the ameloblastoma originate and involve skeletal tissues (mandible and maxilla). This is made possible by tumour cell secretion of paracrine factors that stimulate bone resorption.¹⁸ Humoral hypercalcaemia of malignancy via excessive PTHrP production has been the second possible mechanism for hypercalcaemia in ameloblastoma. This was further proven by several published studies that demonstrated PTHrP expression in majority of cases with ameloblastoma.^{19 20} Both mechanisms are believed to contribute to the development of hypercalcaemia in ameloblastoma just like in our patient.

Table 3 Reported cases of ameloblastoma with hypercalcaemia

Author (year reported)	Gender	Age at diagnosis	Primary site	Years to metastasis	Metastatic sites	Tumour recurrence
Ghiam (2013)	Male	17	Mandible	9	Lungs	Yes
Papaioannou (2009)	Female	7	Mandible	45	Lungs	Yes
Cox (2000)	Male	25	Mandible	None	None	Yes
Inoue (1988)	Female	67	Maxilla	1	Lungs	Yes
Madiedo (1981)	Male	54	Maxilla	1	Lungs, liver	Yes
Seward (1975)	Male	16	Maxilla	11	Lungs, liver, spine	Yes

Learning points

- ▶ Hypercalcaemia in ameloblastoma usually confers a more aggressive and recurrent type of tumour that may lead to an increase in propensity to metastasise in the future.
- ▶ Aggressive tumour removal remains to be the most effective way to treat hypercalcaemia in ameloblastoma.
- ▶ More frequent follow-up and metastatic surveillance is warranted for these patients after primary tumour excision.

Contributors TENL saw the patient and wrote most of the paper. CVV conducted the surgery on the patient and gave the surgical aspect on the management of this case. LTA edited the manuscript and gave expert opinion.

Competing interests None.

Patient consent Obtained.

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