Received: 30 July 2020 | Revised: 16 September 2020 | Accepted: 3 October 2020

DOI: 10.1002/ccr3.3443

CASE REPORT

Clinical Case Reports Open Access WILEY

# Recurrent ameloblastoma with both hypercalcemia and BRAF mutation: A case report

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**Abstract**

This case report describes a mandibular ameloblastoma with both *BRAF* V600E mutation and rare hypercalcemia. The patient without distant metastasis underwent subtotal mandibulectomy using double flaps of fibula and anterolateral thigh. A whole body computed tomography scan taken 69 months after surgery revealed neither recurrence nor metastasis.

**KEYWORDS**

ameloblastoma, BRAF V600E mutation, double free flaps, hypercalcemia, PTHrp

## 1 | INTRODUCTION

Ameloblastoma is a rare, benign, locally invasive tumor accounting for approximately 1% of mandibular cysts and tumors.[1] The standard treatment for ameloblastoma consists of wide resection with appropriate margins and reconstruction to avoid high rate recurrence following conservative treatment.[2,3] Studies have reported that ameloblastoma accompanied by hypercalcemia in surprisingly rare cases presented with distant metastasis in the majority.[4-7] The B-Raf proto-oncogene serine/threonine kinase valine substituted by glutamic acid at amino acid 600 (*BRAF* V600E) mutation is a potential target for molecular target therapy in ameloblastomas.[8,9] Herein, we report the postoperative outcomes in a patient with ameloblastoma without distant metastasis accompanied by both rare hypercalcemia and *BRAF* V600E mutation.

## 2 | CASE SERIES

A 49-year-old woman with a past history of two enucleations performed at ages 20 and 27 years, respectively, for an odontogenic mandibular tumor (keratocyst) was referred to our hospital by the previous hospital where she was diagnosed with a suspicious malignancy based on a growing oral tumor.

Examination and palpation performed at the first visit to our hospital revealed right mandibular tumor swelling, and her albumin-corrected calcium level was 10.3 mg/dL (normal range: 8.7-10.3 mg/dL). X-rays showed that the tumor had spread destruction of the right mandible. Enhanced/plane computed tomography (CT) and magnetic resonance imaging revealed that the multicystic tumor with a maximum size of 110 mm spread from the temporal fossa to the mental protuberance without neck lymph node or distant metastasis.

18F-fluorodeoxyglucose positron emission tomography with CT taken from the head to the thighs revealed abnormal uptake in the mandibular tumor, with the maximum standardized uptake being 12.32, without any metastasis. Figure 1 shows the preoperative images.

Pathological diagnosis of the biopsy specimen obtained from the tumor was ameloblastoma (Figure 2A). In addition, we extracted DNA from a formalin-fixed paraffin-embedded specimen and subjected the sample to cycleave polymerase chain reaction, which revealed a *BRAF* V600E mutation (Figure 2B). The method for this analysis has been described in detail elsewhere.[10]

The patient was hospitalized due to elevation of fever, limitation of mouth opening, and dysphagia due to tumor infection at 10 days following the first visit to our hospital. At the hospitalization, the white blood cell count, C-reactive protein level, and albumin-corrected calcium level were 18 190/μl, 16.1 mg/dL, and 10.4 mg/dL, respectively. The patients received various interventions, including antibiotics, abscess puncture, intravenous hydration, and enteral nutrition via nasogastric tube feeding. At 11 days after hospitalization, a pamidronate was administered to treat high levels of parathyroid hormone–related protein (PTHrp, 2.8 pmol/L; normal range: 0-1.1 pmol/L) and uncontrolled hypercalcemia (albumin-corrected calcium: 12.5 mg/dL). At 26 days after hospitalization, subtotal mandibulectomy with tracheostomy and double free flaps reconstruction using fibula and anterolateral thigh were performed under general anesthesia after normalizing the albumin-corrected calcium level. The pathological diagnosis was ameloblastoma with negative surgical margins. Figure 3 shows the surgical images. At 73 days after hospitalization, the patient was discharged after oral take recovery and decannulation. Her albumin-corrected calcium levels according to the hospital day are shown in Figure 4.

Neither recurrence nor metastasis were detected in the clinical findings, X-ray examination, and a whole-body CT scan performed at 69 months after the surgery with reconstruction (Figure 5). According to a previous report on dietary intake scale, the patient had the highest score such as eating peanuts.[11]

## 3 | DISCUSSION

Ameloblastoma of a slow-glowing tumor localizing 80% of the mandible and 20% of the maxilla has a high recurrence rate but rarely metastazes.[2] Recurrence rates of 65% or 11% have been reported in 315 patients undergoing conservative surgery of simple cutting and enucleation or in 503 patients undergoing radical surgery of wide resection with bone margin and reconstruction for ameloblastoma, respectively.[3] A review from 3677 cases with ameloblastoma reported that because >50% of all recurrences occur within 5 years after surgery, postoperative follow-up is the most important of the treatment strategy.[2]

Hypercalcemia of malignancy in reviews is 80% of humoral PTHrp and 20% of osteolytic such as bone metastasis.[12] A previous case report with a review of literature mentioned that five of six cases with ameloblastoma accompanied by hypercalcemia exhibited metastasis such as lung metastasis.[4] Lung metastasis was also detected in a more recent case of ameloblastoma accompanied by uncontrolled hypercalcemia with higher PTHrp levels reported in 2019.[7] Both humoral

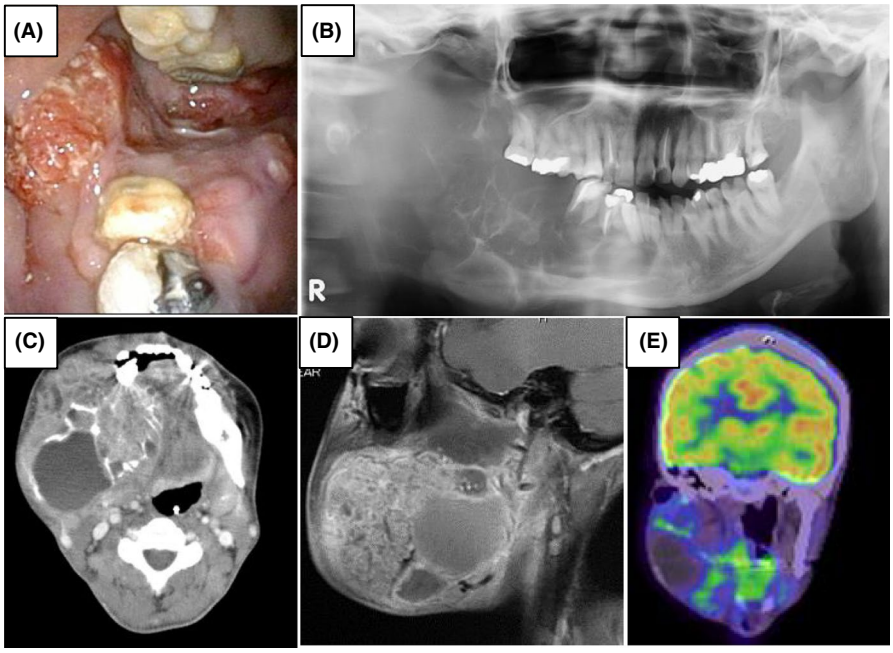


**FIGURE 1** (A) White light image, (B) orthopantomogram radiograph, (C) enhanced computed tomography, (D) enhanced magnetic resonance imaging, and (E) 18F-fluorodeoxyglucose positron emission tomography with computed tomography in mandibular ameloblastoma

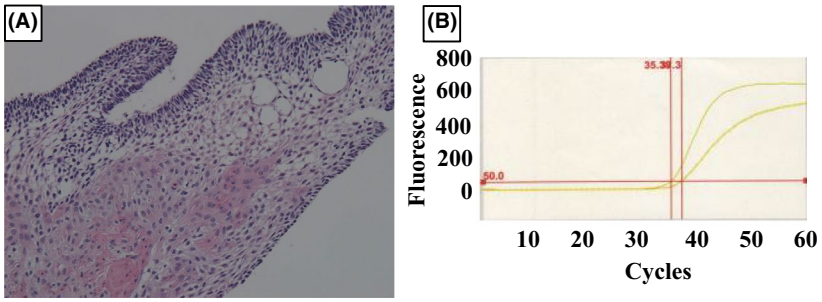


**FIGURE 2** (A) Hematoxylin and eosin staining as well as (B) cycleave polymerase chain reaction for mandibular ameloblastoma

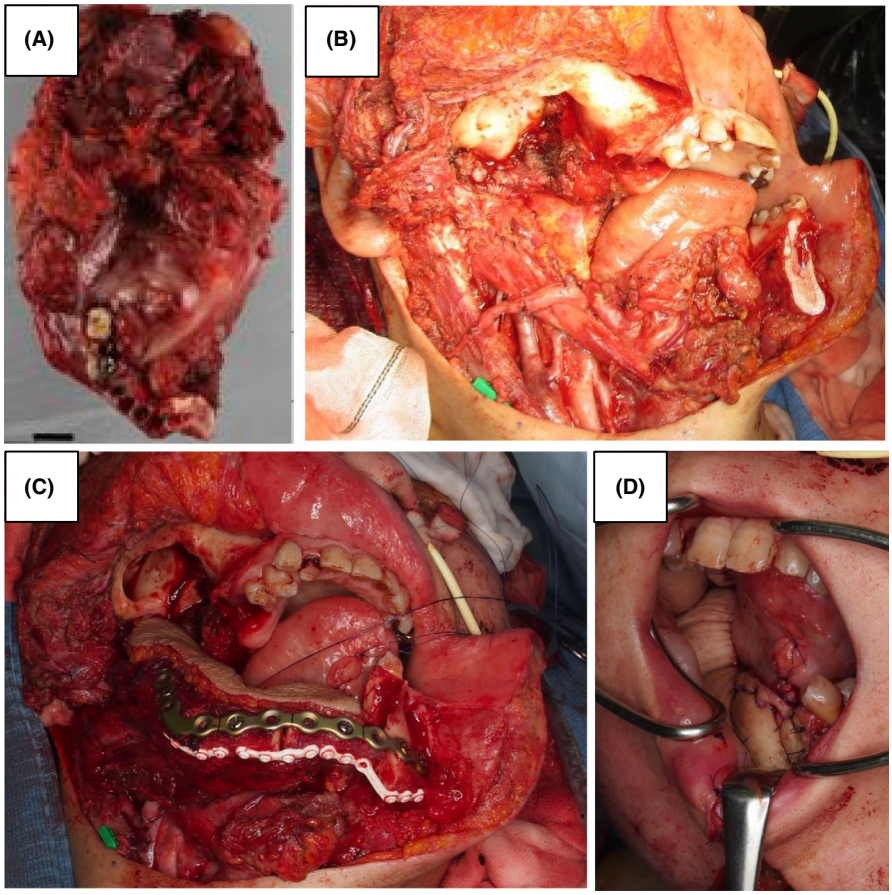


**FIGURE 3** (A) Resected tumor, (B) before reconstruction, (C) after reconstruction by fibula flap, and (D) after reconstruction by fibula and anterolateral thigh flaps at surgery

excessive PTHrp and local osteolysis were considered as the possible mechanism for hypercalcemia in the present case, as described by Lo TE, et al.[4]

The *BRAF* V600E mutation has been used as a diagnostic and predictive biomarker in various types of tumors such as colorectal cancer.[8-10,13-15] The frequency of *BRAF* V600E mutation has been reported as 62%-63% in patients with ameloblastoma,[13] whereas this mutation is rare in other odontogenic tumors.[16] Therefore, the detection of *BRAF* V600E mutation in the present case genetically supported the preoperative diagnosis of ameloblastoma.

Regarding the aspects of hypercalcemia and treatment strategy in two similar cases following surgery, a 20-year-old patient with ameloblastoma accompanied by hypercalcemia without metastasis was treated with tumor excision and mandibular reconstruction after injection of a pamidronate,[4] and a 32-year-old patient with ameloblastoma accompanied by hypercalcemia was treated with tumor excision and mandibular reconstruction.[6] However, there was no mention of *BRAF* V600E mutation in these cases.[4,6] A recent systemic review reported that *BRAF* V600E mutation correlated with several behaviors of ameloblastomas.[8] For instance, *BRAF* V600E in 93 patients with ameloblastoma was immunohistochemically associated with a strong PTHrp expression.[14] In addition, a significant association between *BRAF* V600E mutation and hypercalcemia was detected in 205 patients with multiple myeloma.[15] As a possibility, we considered that the ameloblastoma accompanied by hypercalcemia in our patient has been caused due to the high expression of PTHrp based on *BRAF* V600E mutation. Further accumulation of cases of ameloblastoma accompanied by rare hypercalcemia,

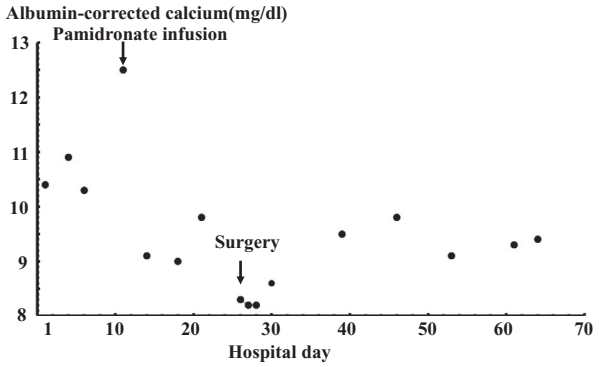


**FIGURE 4** Albumin-corrected calcium levels and hospital day

including *BRAF* V600E mutation, is required. We considered that the present report contributes to the knowledge of a rare ameloblastoma. Tumor with hypercalcemia similar to the present case could happen in other clinical settings. Because PTHrp expression in ameloblastoma was immunohistochemically detected vastly and that was discussed as the expression for enamel epithelium of a developing tooth,[17] it raises the question for PTHrp be broadly used in analysis of ameloblastoma. We thought that the present case without distant metastasis having the possibility of hypercalcemia from ameloblastoma promotes understanding the rare odontogenic tumor.

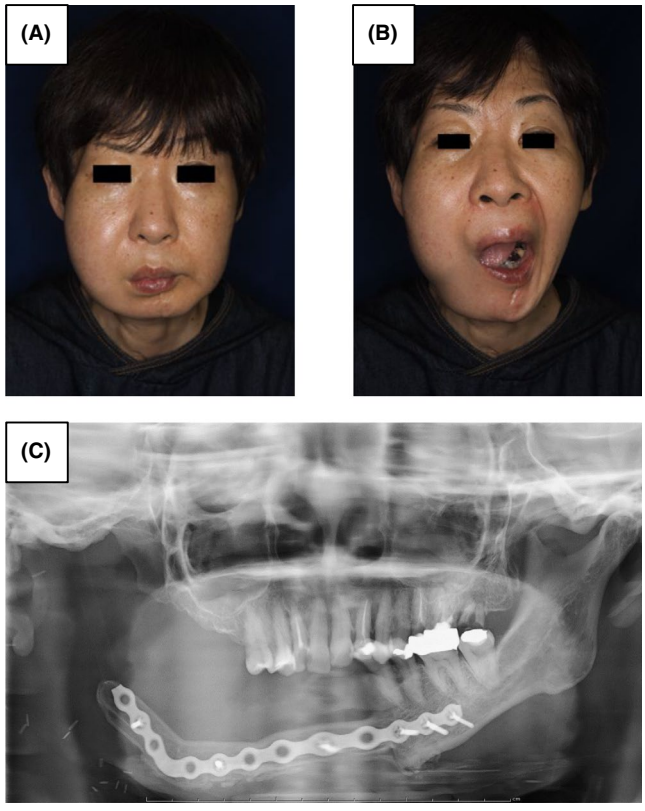


**FIGURE 5** (A) White light image with mouth closing, (B) white light image with mouth opening, and (C) orthopantomogram radiograph at 69 mo after surgery

In conclusion, we report a case of a patient with recurrent nonmetastatic ameloblastoma accompanied by hypercalcemia who was found to have *BRAF* V600E mutation. At 69 months after radical resection using double free flaps of fibula and anterolateral thigh following a pamidronate infusion, the patient showed neither recurrence nor metastasis.

## ACKNOWLEDGMENT

This study was published with written consent of the patient. This case report followed the Declaration of Helsinki on medical protocol and the regional Ethical Review Board of Aichi Cancer Center approved the case report (receipt number: 2020-1-220). This case report has no funding sources. Published with written consent of the patient.

## CONFLICT OF INTEREST

This case report did not receive any findings, and all authors have no conflict of interest to declare.

## AUTHOR CONTRIBUTIONS

HS: contributed main operator of tumor resection and drafted the manuscript and figures. ES: revised the manuscript critically. RN: acquired the data. MS: contributed operation assistance. SH: contributed the manuscript design. IH: contributed main operator of reconstruction. NH: contributed the manuscript design.

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**How to cite this article:** Suzuki H, Sasaki E, Nakamura R, et al. Recurrent ameloblastoma with both hypercalcemia and BRAF mutation: A case report. *Clin Case Rep*. 2020;8:3462–3466. https://doi.org/10.1002/ccr3.3443