**BRAF inhibitor treatment of primary BRAF-mutant ameloblastoma with pathologic assessment of response**

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**Objective.** Molecular characterization of ameloblastoma has indicated a high frequency of driver mutations in BRAF and SMO. Preclinical data suggest that Food and Drug Administration–approved BRAF-targeted therapies may be immediately relevant for patients with ameloblastoma positive for the BRAF V600E mutation.

**Methods.** A neoadjuvant treatment regime of dabrafenib was given to a patient with recurrent BRAF-mutant mandibular ameloblastoma. The patient subsequently underwent left mandible composite resection of the tumor and pathologic evaluation of treatment response.

**Results.** The ameloblastoma had a slow but dramatic response with >90% tumor volume reduction. The inner areas of the tumor underwent degeneration and squamous differentiation, and intact ameloblastoma was present in the outer areas associated with bone.

**Conclusions.** Targeted neoadjuvant therapy for ameloblastoma may be useful in certain clinical settings of primary ameloblastoma. These might include tumors of advanced local stage when a neoadjuvant reduction could alter the extent of surgery and instances of local recurrence when surgical options are limited. (Oral Surg Oral Med Oral Pathol Oral Radiol 2016; -:e1-e3)

Ameloblastoma is an uncommon odontogenic tumor of the mandible or maxilla that rarely metastasizes but has a propensity for local invasion and recurrence.1 The mainstay of treatment is surgery. In spite of the significant morbidity, radical excision and bone reconstruction are preferable to conservative enucleation because of the high recurrence rate associated with conservative enucleation. The role of systemic therapy is ill defined because of the rarity of the disease and limited experience. However, recent progress has been made in the molecular characterization of ameloblastoma, with studies reporting a high frequency of BRAF V600E (valine→glutamic acid substitution at amino acid 600) activating mutations in ameloblastomas,2-4 opening the doors to new molecular-based therapies.

**CASE REPORT**

We present here a case involving an 85-year-old patient who initially developed a lump in his mandible, associated with bleeding around teeth numbers 18 and 19. A computed tomography (CT) scan of his facial bones was performed, indicating a 40-mm left mandibular osteolytic lesion containing enhancing soft tissue in the internal components, with the radiologists favoring ameloblastoma. A week later, he underwent an enucleation of the tumor with bone grafting. Pathologic examination rendered a diagnosis of a gnathic ameloblastoma, including follicular and plexiform patterns, with foci of squamous differentiation that did not meet the requirements for the acanthomatous variant. The patient chose to be followed without further intervention. A 4-month follow-up imaging study indicated regrowth of the tumor in his mandible. Soon after, the patient developed a pathologic fracture at that site. He elected to continue to be followed without further surgical intervention.

For the next year, he was clinically stable without change in symptoms. The patient re-presented after hearing of new treatments for ameloblastoma. He was noted to have a 4.5 cm tumor in the left angle of the mandible (Figure 1A). He consented to having his original ameloblastoma sample tested for BRAF mutations. A BRAF mutational analysis by allele-specific polymerase chain reaction using a Clinical Laboratory Improvement Amendments certified test revealed the presence of a BRAF 1799T:A mutation corresponding to the V600E amino acid substitution. The patient then chose to undergo BRAF V600E inhibitor therapy.

A treatment regime of dabrafenib 150 mg orally (PO) every 12 hours (q12h) was initiated. During the course of therapy,

**Statement of Clinical Relevance**

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the patient developed low energy; noticed more prominent early plaque-like skin lesions (thought to be actinic keratoses) on his face, back, and scalp; complained that his voice was becoming thickened. After 73 days of treatment, the patient elected to discontinue dabrafenib therapy. At that time, he noted an increase in tenderness and swelling of the left jaw. Follow-up CT imaging 2 days after the end of his regimen indicated that the tumor size was unchanged and that there was air present within the lesion (Figure 1B). A month and a half later, the patient underwent a left mandible composite resection of the tumor with titanium plate placement and pectoralis major skin paddle.

Gross pathologic analysis of the resection specimen indicated a 5.5 × 3.5 × 3.2 cm cystic lesion with subcentimeter firm nodules scattered along the cyst wall (Figure 1C). Microscopic sections of the cystic lesions had areas of degeneration with a neutrophilic infiltrate at the luminal aspect of the cyst. In areas not adjacent to the subcentimeter nodules, the intact lumen was lined by epithelium demonstrating squamous differentiation with subluminal cysts (Figure 1D). Intact ameloblastoma with areas of squamous differentiation was present in the subcentimeter nodules and in adjacent bone (Figure 1E). Comparison with the prior enucleation specimen indicated substantially greater areas of squamous differentiation in the treated specimen. The pattern of treatment response was oriented to the cyst wall, with the inside cyst lining undergoing degeneration and squamous differentiation, whereas intact ameloblastoma was present in the outer tissues. From the estimated 50 cm³ tumor volume at the initiation of therapy, <10% of morphologically unaltered ameloblastoma remained.

The enucleated and treated ameloblastoma specimens were assessed for proliferation and BRAF V600 expression by immunohistochemistry. Both the enucleated and treated ameloblastoma specimens had strong mutant BRAF V600E expression. However, in areas of squamous change in the treated specimen, BRAF V600E expression was lower than in similar squamous areas of the enucleation specimen. In both tumors the proliferative index, as measured by Ki67 immunostaining, was low. The proliferative index appeared to be higher in the unaltered areas of the treated ameloblastoma (10%) than in the initial, untreated enucleation sample (5%).

**DISCUSSION**

Here we report both the treatment of a primary mandibular BRAF-mutant ameloblastoma with a BRAF inhibitor (dabrafenib) and the pathologic evaluation of the treatment response. The response that we observed may be similar to the previously reported response of metastatic ameloblastoma of the lung to dual inhibitor therapy. In that case report there was a complete disappearance of fluorodeoxyglucose activity in 8 weeks. The tumor response to treatment in our case did not appear to be as quick. After 10 weeks of therapy there was only a modest radiographic response (Figure 1A vs Figure 1B). However, after a total of 16 weeks from the beginning of therapy, the tumor had a dramatic response with >90% tumor volume reduction. These unusual response dynamics are perhaps due to 2 features of ameloblastoma. First, ameloblastomas have a relatively low proliferation index compared with more common and commonly targeted carcinomas that respond to neoadjuvant therapy, consistent with a slower clinical response. Second, the mutational burden of these tumors is thought to be much lower than common carcinomas. Ameloblastomas with BRAF mutation are likely heavily reliant on the BRAF-activated MAPK pathway for proliferation and survival because there are likely to be few if any other oncogenic mutations. As such, ultimately few cells are likely to escape the effect of BRAF inhibition through pre-existing alternative oncogenic pathways.

The pattern of neoadjuvant response to dabrafenib seen in this particular case of primary ameloblastoma is remarkable in 2 ways. Macroscopically, the bulk of the response within the soft tissue component was more centrally located, leaving a rim of viable tumor surrounding a cystic space. Additionally, tumor within bone appeared to be less responsive. This is in contrast to typical neoadjuvant responses that appear to be more spatially homogeneous. On a cellular level, the treatment appears to have pushed the neoplastic cells to mature to a squamous phenotype. These findings are consistent with observations of squamous differentiation in response to Hedgehog inhibitors in basal cell carcinomas, which share oncornogenesis and onco-oncogenesis with ameloblastoma with respect to their common biology of epidermal placodes (the miniorgans that generate both teeth and hair).
In this instance, clinically significant amounts of viable tumor remained after treatment. This raises the question of whether neoadjuvant treatment could be useful for ameloblastoma. As mentioned earlier, it is possible that either a dual-targeted therapy or a longer treatment period might induce a complete pathologic response. Nevertheless, a partial response might be useful in certain clinical settings of primary ameloblastoma. These might include tumors of advanced local stage when a neoadjuvant reduction could alter the extent of surgery and instances of local recurrence when surgical options are limited. Whether a gene-targeted treatment approach with SMO-mutant ameloblastoma can achieve a significant clinical response remains to be seen.

REFERENCES

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