Treatment of a BRAF V600E Positive Ameloblastoma in a Pediatric Patient with MEK Inhibitor Monotherapy

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Abstract
Ameloblastomas are uncommon tumors of the odontogenic epithelium standardly treated with radical resection. Recent studies of the genetic landscape of ameloblastoma have revealed the frequent presence of the BRAF V600E mutation, suggesting a possible role for targeted chemotherapy. We present the case of a primary mandibular ameloblastoma found in a 13-year-old female with confirmed BRAF V600E mutation. Prior to invasive surgical intervention she was treated for 8 weeks with the MEK inhibitor trametinib, but her tumor demonstrated little radiographic, clinical, or histologic response. Previous case reports have shown ameloblastoma in adult patients to be responsive to other agents targeting the MAPK pathway. Our observations in the presented case demonstrate the need for further research into the utility of targeted chemotherapy in ameloblastoma treatment.

Keywords
ameloblastoma, chemotherapy, pediatrics

Introduction
Ameloblastoma is a rare, benign neoplasm of the odontogenic epithelium. These lesions demonstrate a predilection for the posterior mandible, are locally destructive, and have a high rate of recurrence. Standard definitive treatment is complete bony resection with a substantial margin of safety, often resulting in significant morbidity.1 Historically, little has been known about the molecular pathogenesis of these tumors. In 2014, Kurppa et al2 first reported the high frequency of BRAF V600E mutations in 63% of ameloblastomas analyzed by cDNA sequencing, with subsequent independent studies also reporting a high frequency of BRAF mutations in 46% to 63% of tumors.3,4 Eningen studies in a variety of patient populations have further expanded on the frequency and variation of this mutation in ameloblastoma cell lines and tumor specimens.5-9 Fregnani et al10 found that BRAF V600E mutation correlates with more aggressive behavior as measured by recurrence, multilocular radiographic appearance, and disruption of basal bone. Investigations by Brown et al3 and Kelppe et al7 found the mutation to be associated with earlier age of occurrence, though studies by other groups found no such association.5,6,8,11 Multiple reports have noted that the BRAF V600E mutation appears almost exclusively in mandibular lesions.3,4,11

BRAF V600E mutation is well documented in a variety of neoplasms including melanoma, papillary thyroid cancer and colorectal cancer. Multiple drugs are available to treat these diseases by targeting the aberrant MAPK pathway.12 The discovery of frequent BRAF V600E mutation in ameloblastomas suggests a possible therapeutic use of these small-molecule inhibitors in management of the disease, and a potential shift in the treatment of ameloblastoma toward a personalized medicine paradigm.13 In vitro studies have demonstrated the sensitivity of ameloblastoma cell lines to the BRAF inhibitor vemurafenib, and 2 case reports have shown good clinical response to the agent.3,4,14,15 Similarly, there have been reported cases of ameloblastoma responding to the BRAF inhibitor dabrafenib, as well as to dual BRAF/MEK inhibition with dabrafenib/trametinib.16-19 Here we present the case of a primary ameloblastoma in a pediatric patient that was treated with neoadjuvant single-agent MEK inhibitor therapy prior to any invasive surgical intervention.

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Case Report

A 13-year-old African-American female presented with her mother to our clinic for evaluation of a visually-appreciable right mandibular swelling. She reported experiencing moderate associated pain for 1 year and no paresthesia. Per her mother, the patient had no prior medical or surgical history and was taking no medications. An orthopantogram was obtained which demonstrated a radiolucent unilocular mass encompassing the right mandibular angle, coronoid process, and condylar neck with significant displacement of teeth #31, 32 (Figure 1). She had visited a local emergency room 6 weeks previously for this chief complaint where a maxillofacial CT scan was obtained prior to discharge. On review it similarly demonstrated a 4.0 cm × 2.8 cm × 5.5 cm expansile fluid attenuation with incomplete septations associated with tooth #32, favored by the radiologist to represent a dentigerous cyst. The patient was promptly placed on oral clindamycin and an incisional biopsy was performed in our clinic under intravenous sedation 1 week later. Microscopic examination of this biopsy revealed a benign neoplasm of odontogenic differentiation, with predominantly cystic architecture and occasional invasive tumor islands in the cyst wall. These islands demonstrated palisading and reverse polarity, and were surrounded by hyalinized stroma. A diagnosis of ameloblastoma was made. Subsequent genomic analysis by allele-specific polymerase chain reaction showed that the lesion harbored a BRAF 1799T:A amino acid substitution, corresponding to an activating V600E mutation.

Consideration was given to utilizing neoadjuvant MAPK pathway inhibitor therapy in an effort to reduce the morbidity of subsequent surgery or avoid surgery entirely for this patient. She was referred to pediatric hematology/oncology, and per their protocol, was planned for daily oral 1.5 mg trametinib therapy beginning 8 weeks following biopsy. Immediately prior to beginning chemotherapy a maxillofacial CT showed the lesion to have grown to 3.4 cm × 3.2 cm × 6.4 cm with marked thinning of the mandibular cortex. After 2 weeks of chemotherapy the patient experienced modest pustular facial acne, the drug was held for a 1 week period, and then restarted at a reduced dosage of 1 mg daily. After 6 more weeks of continued chemotherapy, a maxillofacial CT scan was obtained which demonstrated the lesion to have been largely unresponsive, measuring 3.3 cm × 3.2 cm × 6.3 cm (Figure 2), with a slight improvement in cortication. The patient and her mother reported no subjective improvement at that time, and after discussing treatment options they elected to proceed with surgical resection. Right hemimandibulectomy (Figure 3) with immediate left fibula free flap vascularized reconstruction was performed, with post-operative pathology confirming the pre-operative diagnosis of ameloblastoma. The resected gross specimen contained a 6.5 cm × 2 cm × 2.9 cm cystic structure with a focally bosselated lining, and the overlying mandibular cortex was thinned to 0.1 cm. Microscopic analysis of the final resected specimen showed no necrosis, squamous differentiation, or substantial changes in architecture compared to the pretreatment biopsy specimen, further indicating a lack of response to the

Figure 1. Orthopantogram obtained on initial presentation.

Figure 2. Maxillofacial CT prior to trametinib therapy (A) and after 8 weeks of trametinib therapy (B).
trametinib. The patient experienced an uncomplicated postoperative course. Serial follow-ups for 3 months and postoperative imaging showed appropriate healing of operative sites with no signs of local recurrence.

Discussion

The use of MAPK pathway inhibitors in treating ameloblastoma is still in its infancy, and the optimal agent or combination of agents has yet to be determined. BRAF inhibitor monotherapy is associated with promotion of secondary malignancy due to activation of wild-type RAF proteins, which is a particularly concerning adverse reaction in an adolescent.30 Trametinib targets the MAPK pathway downstream of BRAF by inhibiting MEK. Dual-therapy with BRAF and MEK inhibitors has been shown to reduce, but not eliminate, promotion of secondary malignancy compared to BRAF inhibitor monotherapy.21,22 Toll et al24 reported 3 cases of glioma in children treated successfully with combination BRAF/MEK inhibition, and no secondary malignancies were noted. While this does provide some early evidence for the safety of combination therapy in the pediatric population, it is certainly a limited sample. Several similar, higher-powered reports have shown the efficacy and safety of trametinib monotherapy in treating neurofibromas and gliomas in the pediatric population as well.25-30 Trametinib is approved by the United States Food and Drug Administration as monotherapy for treatment of melanoma and has not been demonstrated to drive secondary malignancy, which made it potentially the most ideal choice for our patient.31 Additionally, the pediatric oncologist treating our patient was exceedingly familiar with the agent, and therefore preferred its selection, feeling best able to manage dosing adjustments and side effects.

We report a case of BRAF V600E positive ameloblastoma in a pediatric patient treated unsuccessfully with neoadjuvant MEK inhibition as determined by radiographic, clinical, and histologic criteria. In previous case reports involving ameloblastoma, significant improvement was observed after less than 1 month of targeted MAPK pathway inhibition, so we believe our 8-week trial to have been adequate.14,16,18 The presented case is unique in several respects including age of patient, stage of disease at intervention, and chemotherapeutic agent. Conservative management of ameloblastoma is often considered in pediatric patients due to the sequelae of bone removal during growth phase and the psychosocial ramifications of radical resection. As was true in the presented case, pediatric patients would benefit greatly from neoadjuvant therapies that improve the success of conservative treatment, alleviate tumor burden, or reduce surgical morbidity. Standard dosing of oral trametinib is 2 mg daily, which was the dose used in combination with dabrafenib in the adult cases of ameloblastoma reported by Kaye et al18 and Brunet et al.19 In the presented pediatric case, the dose was adjusted to 1.5 mg daily, with the intention of increasing to 2 mg daily depending on patient tolerance. As mentioned, the dose was soon reduced to 1 mg daily after the patient experienced a mild adverse drug reaction. It is possible that this dosage was ultimately subtherapeutic, which may hold implications for the utility of neoadjuvant MAPK pathway inhibitors in the pediatric population. This could prove to be particularly relevant if the disputed finding that BRAF V600E is associated with younger age of incidence is validated. Our case is the first reported attempt to treat a primary lesion with MAPK pathway inhibition, all other reports have involved recurrent or metastatic disease.14,19 This is also the first reported case of treating ameloblastoma with MEK-inhibition monotherapy. Our hope was that given the young age of this patient, she could be spared major reconstructive surgery. Ultimately the lack of significant disease response to our neoadjuvant intervention further illustrates the need for research into the efficacy and appropriate dosing of targeted therapy for BRAF-mutant ameloblastoma.

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