LETTERS TO THE EDITOR

Regarding BRAF-inhibitor therapy of primary ameloblastoma

To the Editor:

Tan et al.1 describe the use of dabrafenib in the management of a primary intraosseous BRAF V600E mutant ameloblastoma prior composite surgical resection, as a single case report. Although this potentially represents a novel approach to management for some cases of ameloblastoma, inclusion of several additional data points would be instructive. At initial presentation, the 4-cm mandibular lesion was enucleated, immediate bone grafting performed, and the diagnosis of ameloblastoma subsequently established. The patient declined further surgery, but details of the surgical plan are not specified. The article identifies the ameloblastoma as recurrent, but the “regrowth” identified on computed tomography (CT) performed 4 months after the enucleation procedure suggests that this is persistence of the original tumor, as enucleation is not regarded as definitive management for conventional (classic/multicystic) ameloblastoma. In some cases, the distinction between recurrent and persistent tumors may not alter surgical therapy, but if it evolves into important patient selection criteria for targeted drug therapy of ameloblastoma, the distinction, where possible, seems relevant.

Soon after the 4-month interval CT, a pathologic fracture is reported to have been identified; however, the patient elected to be followed up without intervention, only to present again approximately a year later after hearing about “new treatments for ameloblastoma.”2 Dabrafenib was initiated and continued for 73 days until it was discontinued by the patient, although the original plan for assessment of response and duration of therapy is not specified in the report. Cross-sectional imaging obtained after drug discontinuation identified air within the lesion, but the significance of the radiographic finding was not elaborated. If the presence of air within the lesion suggests communication with the oral environment or communication with the facial skin via progression of the known pathologic fracture, the Pathology team might expect to find a corroborating inflammatory response in the submitted pathology samples, which, in some areas, could alter classic histopathologic findings (Figure 1).

The authors noted that the patient’s radiographic response to targeted therapy seemed to lag in comparison with a published report3 of a patient who had ameloblastoma as a child and had undergone resection and reconstruction of the mandible. The patient described in the report by Kaye et al. had experienced multiple episodes of recurrent tumor over a period spanning decades, leading to local field radiation therapy for an unresectable mandibular recurrence and, ultimately, the development of symptomatic lung metastases. Additionally, the patient had completed dual therapy with dabrafenib and trametinib over a 20-week period, and the radiographic response to the targeted drug therapy was highlighted with positron-emission tomography/CT.3 Differences in the extent and course of disease, described symptoms, methods of radiographic assessment, type of targeted therapy, and drug duration, in our opinion, preclude meaningful comparison between these two cases.

Upon pathologic examination of the resection specimen, Tan et al.,1 identified squamous differentiation histologically and suggest an association with the effect of neoadjuvant therapy. Although not required for diagnosis, the neoplasm was not resampled to assess or establish a baseline microscopic appearance (subsequent to the placement of bone graft, or pathologic fracture) before initiation of dabrafenib. Alternative explanations for the presence of squamous differentiation in the BRAF-mutant tumor could include exposure to air as identified by CT criteria and/or secondary infection and inflammation resulting from oral communication or pathologic fracture. The nature of the bone graft material placed at the time of the enucleation procedure was not stated in the report; however, the placement of exogenous material within the defect cavity could also result in tumor irritation and/or infection, as well as reactive tumor changes.

The neoplasm before and after drug treatment was described as having “strong mutant BRAF V600E expression”4 in areas of classic tumor morphology, as assessed by immunohistochemical staining. Immunohistochemical assessment of BRAF expression has not been well described in ameloblastoma, and therefore further characterization of the pattern or localization of expression and supplementation with photomicrographs are essential for complete understanding of the reported result.

A composite mandibular resection was performed after the cessation of dabrafenib, but the extent of the surgical resection was not described, the assessment of final margin status was omitted, and the period of postoperative follow-up was not specified. The sparseness of clinical and radiographic details, as characterized above, makes it impossible to assess if the resection was identical, similar to, or perhaps distinctly different from the surgical procedure the patient was originally offered.
once the diagnosis of ameloblastoma was confirmed, or in the setting of the post-enucleation pathologic fracture. The authors noted that the “tumor within bone appeared to be less responsive.” In the vast majority of cases, ameloblastoma occurs within an intraosseous location; therefore, this is an important observation. There is insufficient evidence to suggest that neoadjuvant drug therapy results in the predictable or organized “shrinkage” of ameloblastoma within bone to permit consideration of a reduction in the extent of surgical resection. The above-mentioned observation made by the authors appears to underscore the importance of planning definitive surgery based on the original clinical-radiographic presentation of a primary, surgically resectable, benign intraosseous ameloblastoma.

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BRAF inhibitor therapy of primary ameloblastoma

To the Editor:

We thank the reader for the interest in this case report. Our case report represents the first pathologic description of ameloblastoma response to BRAF inhibitor therapy. We would note that the primary goal of our case report was not to provide an integrated evaluation of the efficacy of BRAF inhibitor therapy of primary ameloblastomas. That is something that is better served by a prospective clinical trial. Our observations are based on a single case, with a comparison with a prior case report that bears some similarities.

Here, we provide more clinical detail as requested by the reader. The resection planned and performed was that of the subcondyle, ramus, and posterior alveolar ridge, preserving the more anterior teeth. This composite resection was not different from that which would have been performed once the diagnosis of ameloblastoma was confirmed. After anti-BRAF treatment, air within the lesion was noted on computed tomography (CT) imaging. This could represent communication with a mucosal surface as a result of necrosis of the tumor. The bony defect at enucleation was not reconstructed because of the patient’s age; instead, occlusion was maintained via a titanium plate, and the soft tissue was reconstructed with a pectoralis major flap that wrapped around the prefashioned plate. The final margin status was clinically negative,