Journal of Dental Sciences 19 (2024) 1892–1893

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journal homepage: www.e-jds.com

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Novel *NRAS* G12D mutation in extraosseous/peripheral ameloblastoma: Case report and review of mitogen-activated protein kinase pathway mutations in extraosseous/peripheral and intraosseous ameloblastomas

KEYWORDS
Extraosseous ameloblastoma;
Peripheral ameloblastoma;
NRAS G12D;
MAPK pathway;
Next-generation sequencing

Extraosseous/peripheral ameloblastoma (EPA) is a rare type of benign odontogenic tumor. Although occurring in different anatomical locations, EPA shares both histologic and molecular features with intraosseous ameloblastoma.[1,2] Expanding the genetic landscape of ameloblastoma may further the understanding of the molecular basis of its pathogenesis and provide insights into potential therapeutic targets. The aim of this study was to report a novel mutation found by next-generation sequencing in EPA and to briefly review mitogen-activated protein kinase (MAPK) pathway mutations shared between intraosseous and extraosseous ameloblastomas.

Whole-exome sequencing was performed in a case of EPA arising in the mandibular alveolar mucosa of a 65-year-old male (Fig. 1A) by using the SureSelect Human All Exon V8 (Agilent Technologies) as described previously.[3] As a result, the *NRAS* p.G12D (c.35G > A) mutation was detected, and no other MAPK pathway mutations were found. For further analysis, primers for polymerase chain reaction and Sanger sequencing were designed to amplify exon 2 of the *NRAS* gene (forward: 5′-CAACAGGTTCTTGCTGGTGT-3′, reverse: 5′-CCTCACCTCTATGGTGGGAT-3′), and the *NRAS* p.G12D (c.35G > A) mutation was identified (Fig. 1B). To confirm the activation of the MAPK pathway, immunohistochemistry for phosphorylated extracellular signal-regulated kinase (p-ERK) was performed as described previously;[4] most tumor cells showed strong nuclear expression of p-ERK (Fig. 1C). These findings indicate that previously unidentified *NRAS* G12D mutations can be found in EPA, mutually exclusive with known genetic alterations, and may lead to activation of the MAPK pathway.

Most of the mutations reported in EPA to date are involved in the MAPK pathway, including *BRAF* V600E, *NRAS* Q61R, and *FGFR2* C382R mutations.[1,2] In addition to these mutations, more diverse MAPK pathway mutations have been identified in intraosseous ameloblastoma compared with EPA, such as *KRAS* G12C, *KRAS* G12R, *NRAS* Q61K, *HRAS*

https://doi.org/10.1016/j.jds.2024.05.010

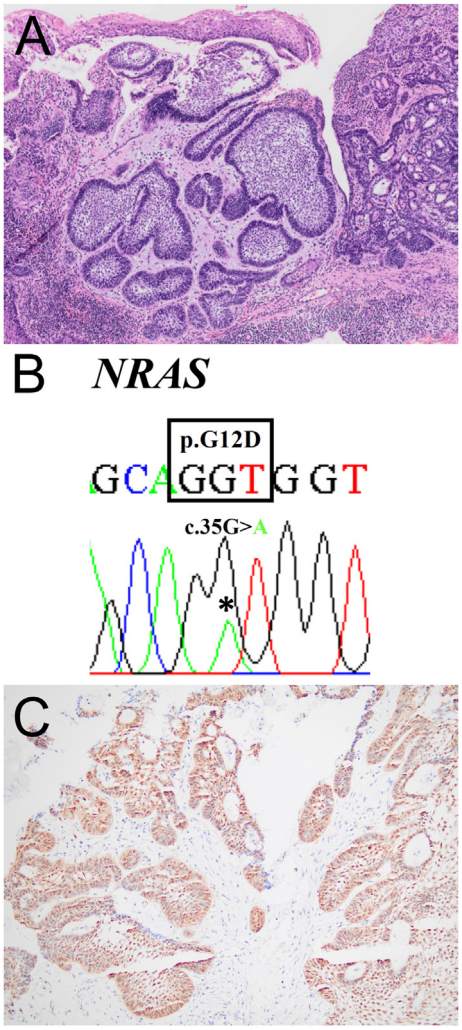

Figure 1 Histologic, immunohistochemical, and molecular findings of a case of extraosseous/peripheral ameloblastoma. (A) Islands of ameloblastic epithelium are found underneath the surface mucosal epithelium (H&E). (B) The *NRAS* p.G12D (c.35G > A) missense mutation (asterisk) is confirmed by Sanger sequencing. (C) Phosphorylated extracellular signal-regulated kinase (p-ERK) immunohistochemistry shows strong and diffuse staining in the nuclei of tumor cells.

Q61K, *HRAS* Q61R, and *FGFR2* V395D mutations;[1,4] however, there is considerable overlap in molecular features between EPA and intraosseous ameloblastoma: (1) The majority of genetic alterations are found in the MAPK pathway. (2) Among MAPK pathway genes, *BRAF* is the most frequently mutated gene, with the V600E variant accounting for almost all cases. (3) MAPK pathway mutations are associated with MAPK pathway activation in a tissue context, as demonstrated by p-ERK immunohistochemistry in our previous[4] and present studies.

According to the Catalogue of Somatic Mutations in Cancer (COSMIC) database (https://cancer.sanger.ac.uk), *NRAS* G12D mutations are most commonly reported in leukemia, followed by colorectal adenocarcinoma and malignant melanoma. Although drugs directly targeting *NRAS* mutations are not currently approved (https://www.fda.gov/drugs), a patient with *NRAS* G12D-leukemia showed a near-complete response to trametinib, a MEK inhibitor.[5] Therefore, the *NRAS* G12D mutation newly identified in ameloblastoma in this study may represent a new potential therapeutic target for patients with advanced ameloblastoma.

Declaration of competing interest

The authors have no conflicts of interest relevant to this article.

Acknowledgments

None.

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Received 7 May 2024
Final revision received 9 May 2024
Available online 15 May 2024