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IMAGE

Pleomorphic Adenoma of the Palate with Bizarre Ductal and Myoepithelial Cells: A Case Image

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Abstract

Background Pleomorphic adenomas (PAs), the most common salivary gland tumors, are comprised of ductal epithelial and myoepithelial cells within a stromal background. A rare subset of PAs exhibits bizarre cells and 12q amplification involving *HMGA2* and *MDM2*; in reported cases, bizarre cells have been confined to the myoepithelial component. We report the first case of a PA with bizarre-cytological features in both the ductal and myoepithelial components.

Case presentation A 75-year-old woman presented with a palatal mass. Histology revealed a well-circumscribed biphasic tumor with marked nuclear pleomorphism in both luminal ductal and non-luminal myoepithelial cells. Despite the alarming atypia, mitotic activity was low, and neither necrosis nor invasive growth was observed. Immunohistochemically, luminal bizarre cells exhibited ductal characteristics, whereas non-luminal bizarre cells exhibited myoepithelial characteristics. Tumor cells were negative for androgen receptor and HER2 and showed a p53 wild-type expression pattern. The Ki-67 labeling index was <5%, and the bizarre cells rarely tested positive. Molecular analysis demonstrated amplification of *HMGA2* and *MDM2*, whereas no other pathogenic variants related to salivary gland tumors were detected. Complete excision was performed; no evidence of recurrence or metastasis was observed after 10 months.

Conclusion Marked cytological atypia of bizarre cells in PA, even when involving ductal cells, may not necessarily indicate malignancy. This case highlights the value of integrating clinicopathological and genetic findings to better define PAs with bizarre cells and prevent overdiagnosis of carcinoma based on atypia alone.

Keywords Salivary glands · Pleomorphic adenoma · 12q · *HMGA2* · *MDM2*

Abbreviations

FISH	Fluorescence in situ hybridization
HMGA2	High-mobility group AT-hook 2
MDM2	Mouse double minute homolog 2
NGS	Next-generation sequencing
PA	Pleomorphic adenoma

Pleomorphic adenoma (PA), the most common salivary gland tumor, is comprised of ductal epithelial and myoepithelial cells within a stromal background and is arranged in various morphological patterns [1]. Although PAs are benign, they may contain neoplastic cells with varying degrees of atypia [1, 2]. Bishop et al. [2] proposed a PA subset based on an analysis of salivary gland tumors with

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tumor cells showing high-grade nuclear atypia termed "bizarre cells." This subset is characterized by 12q amplification involving *HMGA2* and/or *MDM2*, bizarre cells with myoepithelial properties, and biphasic tumor architecture [2]. To date, only 13 cases of PA featuring bizarre cells have been reported (Supplementary Tables 1, 2); in all cases, the bizarre cells were confined to the myoepithelial component [2–5]. Herein, we report the first case of palatal PA with bizarre-cytological features in both the ductal epithelial and myoepithelial components.

A 75-year-old woman was referred to Osaka University Dental Hospital for painless swelling of the left side of her hard palate persisting for 6 months. She had no history of smoking or alcohol consumption, or notable medical history. Intraoral examination revealed a bluish mass (Fig. 1a). Imaging showed a well-circumscribed, ovoid submucosal mass measuring 14 × 13 × 12 mm (Fig. 1b) and pressure-induced resorption of the adjacent maxillary alveolar bone (Fig. 1c). Based on a clinical diagnosis of PA or a low-grade malignant salivary gland tumor, an incisional biopsy and complete excision were performed.

Macroscopically, the cut surface of the surgical specimen had solid whitish and yellowish areas (Fig. 2a, b). Histologically, the whitish areas corresponded to a well-circumscribed proliferation of tumor cells adjacent to the salivary glands, without a distinct capsule (Fig. 2c). The yellowish areas corresponded to macrophage aggregates (data not shown). The tumor showed a proliferation of tumor cells, forming cystic and ductal structures (Fig. 2d). The tumor was composed of an admixture of bilayered ducts, myoepithelial cells, and stroma. Ductal and myoepithelial cells were commonly arranged as bilayered ductal structures, and the luminal ductal cells often exhibited abundant eosinophilic cytoplasm with mild nuclear enlargement (Fig. 2e, f). Bizarre cells were scattered within the inner luminal epithelial layer (Fig. 2f) and in areas of sheet-like proliferation of non-luminal myoepithelial cells (Fig. 2g). The bizarre cells contained large, irregularly shaped nuclei with smudgy chromatin and, occasionally, nuclear vacuoles. The overall mitotic rate was low (~1/10 HPF), and the bizarre cells lacked mitotic activity. Focal mucous cells staining positive for mucicarmine were identified (Fig. 2h). No increase in mitotic figures, atypical mitosis, necrosis, lymphovascular invasion, or perineural invasion were present.

Immunohistochemical analysis (Fig. 3) revealed strong expression of CK AE1/AE3 and CK7 in ductal epithelial cells and weak expression of these in myoepithelial cells. Myoepithelial-cell markers (p63, p40, SMA, and calponin) highlighted preservation of the biphasic architecture. Luminal bizarre cells were strongly positive for CK AE1/AE3 and CK7 and negative for myoepithelial-cell markers, supporting their ductal cell characteristics. Conversely, non-luminal bizarre cells were weakly positive for CK AE1/AE3 and CK7 and positive for myoepithelial-cell markers, supporting their myoepithelial cell characteristics. The Ki-67 labeling index was lower than 5% throughout the tumor. Similar positivity rates were observed in both ductal and myoepithelial cells. However, most bizarre cells tested negative. The tumor cells were negative for androgen receptor and HER2. They exhibited a p53 wild-type expression pattern.

RNA-based targeted next-generation sequencing (NGS) was performed using a custom panel designed to detect fusions, single-nucleotide polymorphisms, insertions/deletions, and expression levels of 27 genes relevant to salivary gland tumors [1] (Supplementary Table 3). It revealed a high expression level of *HMGA2* (Fig. 4a). Similarly,

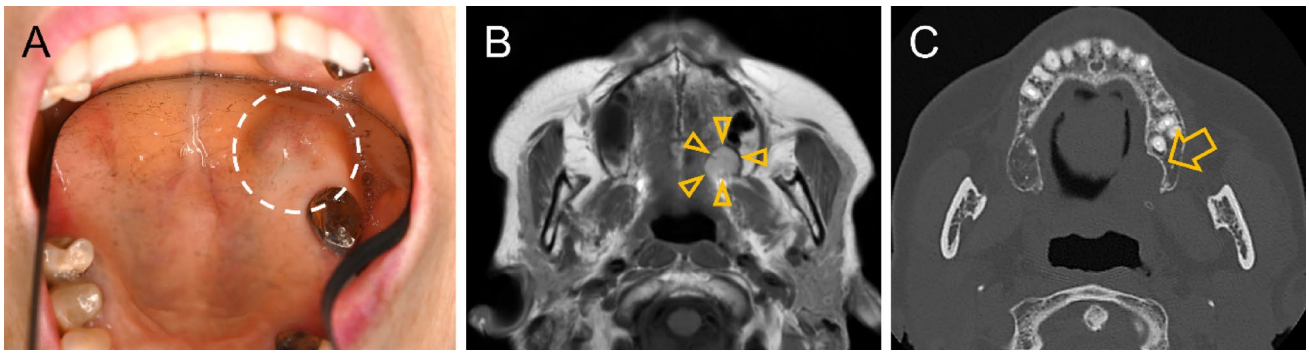


Fig. 1 Clinical and radiological presentation. **a** Intraoral image showing a bluish, dome-shaped mass on the left palate (mirror image). **b** Representative axial T1-weighted magnetic resonance image. The arrowheads delineate the extent of the tumor. **c** Representative axial computed tomographic image with bone window. The arrow indicates pressure-induced bone resorption of the left maxilla adjacent to the tumor

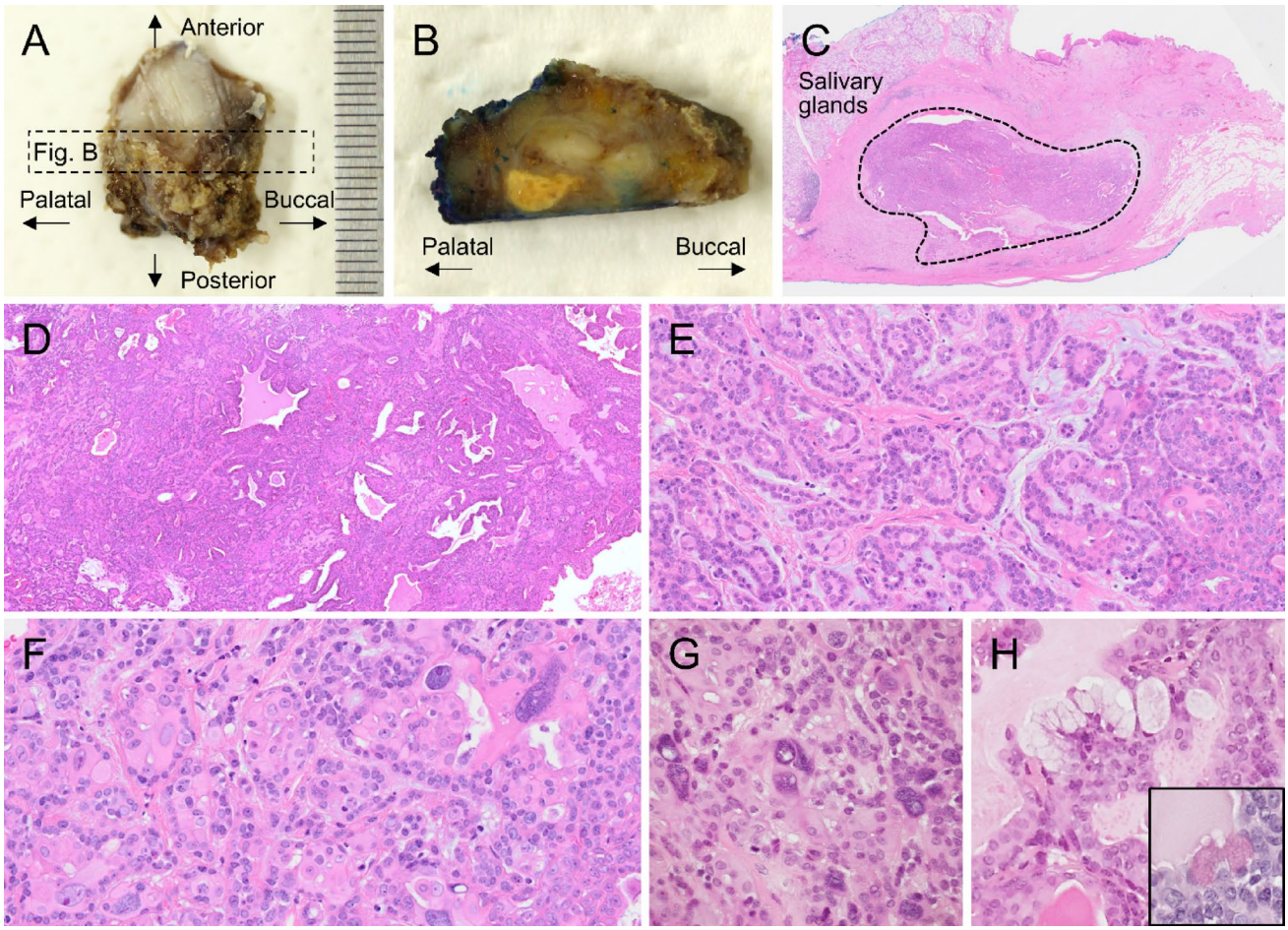


Fig. 2 Histological findings. **a**, **b** Gross view of the resected specimen and cut surface. **c** Corresponding hematoxylin and eosin staining of the cut surface showing a relatively well-circumscribed proliferation of tumor cells adjacent to the salivary gland tissue (tumor area indicated by the dashed line). **d** Low-magnification view showing a proliferation of tumor cells forming variably sized cystic and ductal structures. **e** Medium-magnification view revealing bilayered luminal structures surrounded by myxoid and fibrous stroma. **f** High-magnification view showing bizarre neoplastic cells with enlarged, irregularly shaped nuclei and abundant eosinophilic cytoplasm within the luminal layer. **g** Bizarre cells within non-luminal, sheet-like areas. These bizarre cells exhibit large, irregularly shaped nuclei with smudgy chromatin and occasional nuclear vacuoles, but mitoses are absent. **h** Mucous cells in the luminal layer (inset: mucicarmine stain)

fluorescence in situ hybridization (FISH) demonstrated amplification of *HMGA2* without rearrangement (Fig. 4b). Immunohistochemistry for HMGA2 revealed diffusely positivity in the tumor cells, including the bizarre cells (Fig. 4b). Although *MDM2* was not included in the custom NGS panel, FISH confirmed *MDM2* amplification, and immunohistochemistry showed that the tumor cells, including the bizarre cells, were strongly positive for MDM2 (Fig. 4b). These findings support the presence of 12q amplification in bizarre cells as well. Targeted NGS did not identify other pathogenic variants commonly found in PAs or carcinoma ex-PA [1].

Based on these observations—a biphasic tumor with low proliferative activity, mucinous metaplasia, and an *HMGA2* alteration—a final diagnosis of PA with bizarre ductal and myoepithelial cells was established. Ten months after surgery, no recurrence or metastasis was observed, but authors acknowledge the limited follow-up for this tumor type. The subset of PAs with bizarre cells appears to have a favorable prognosis, suggesting that the presence of these cells may indicate a benign process rather than malignancy [2–5] (Supplementary Table 1). The present case also suggests that the marked nuclear atypia of these bizarre cells, even when present in

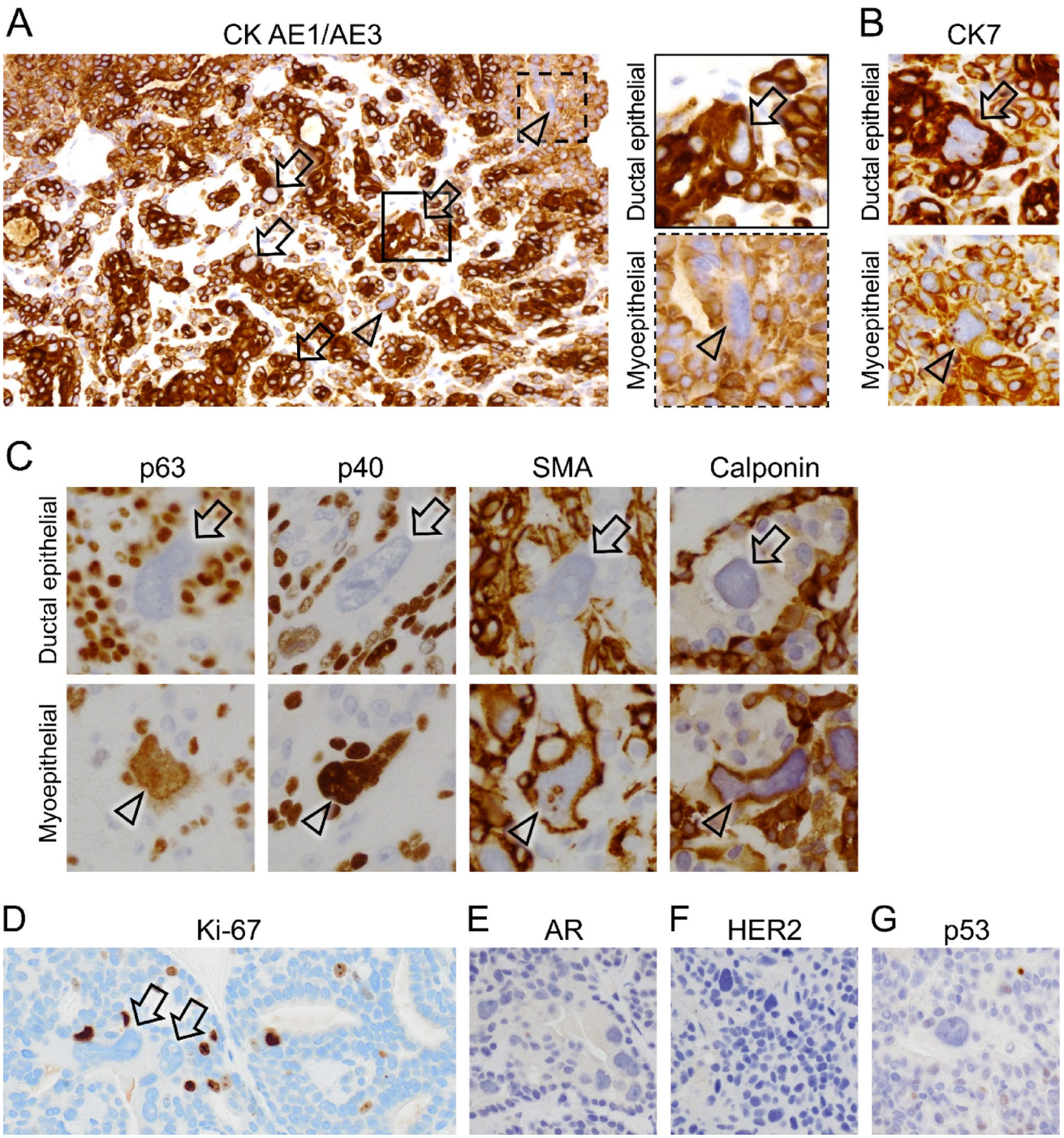


Fig. 3 Immunohistochemical findings. **a** Immunohistochemical staining for CK AE1/AE3. The inset with a solid border shows a higher magnification of bizarre cells with strong CK AE1/AE3-positivity, and the inset with a dashed border shows a higher magnification of bizarre cells with weak CK AE1/AE3-positivity. **b** Immunohistochemical staining for CK7. **c** Immunohistochemical staining for the myoepithelial markers p63, p40, SMA, and calponin. The upper panels show bizarre cells with ductal epithelial characteristics, and the lower panels display bizarre cells with myoepithelial characteristics. Arrows indicate bizarre ductal cells, while arrowheads point to bizarre myoepithelial cells (**a**–**c**). **d**–**g**. Immunochemical staining for Ki-67 (**d**), AR (**e**), HER2 (**f**), and p53 (**g**). Arrows indicate bizarre cells (**d**). SMA, smooth muscle actin; AR androgen receptor

ductal cells, is not necessarily indicative of malignancy, and may be a significant diagnostic pitfall on preoperative biopsy. Detailed clinical, morphological, and genetic analyses may improve our understanding of the biological behavior of PAs and help to avoid a misdiagnosis of carcinoma based on cytological features alone.

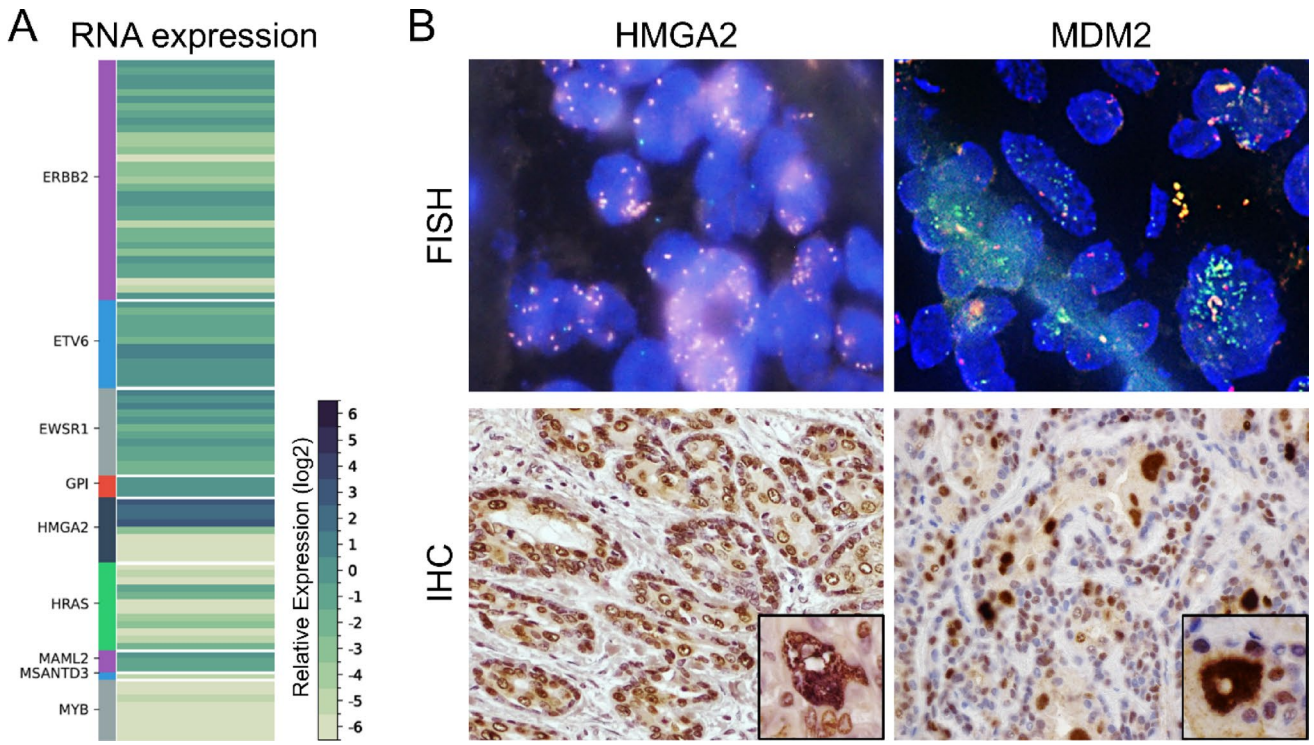


Fig. 4 Molecular analysis. **a** RNA expression levels from RNA-based targeted next-generation sequencing, showing a high expression level of HMGA2. **b** Fluorescence in situ hybridization (FISH; upper panels) and immunohistochemistry (IHC; lower panels). In the left panels, HMGA2 break-apart FISH reveals amplification without rearrangement (5'-red centromeric side, 3'-green telomeric side). IHC showing high HMGA2 protein expression in both ductal and myoepithelial cells (inset shows a bizarre cell). In the right panels, FISH analysis shows MDM2 amplification (green signals) relative to the chromosome 12 centromere control (red signals). IHC shows high MDM2 protein expression in both ductal and myoepithelial cells (inset shows a bizarre cell)

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Author Contributions All authors contributed to this work and reviewed and approved the manuscript for submission. Katsutoshi Hirose designed the study. Katsutoshi Hirose, Masato Nakaguro, Taisuke Mori, and Satoru Toyosawa interpreted hematoxylin and eosin staining and immunohistochemical findings. Katsutoshi Hirose, Masato Nakaguro, and Taisuke Mori performed molecular analysis and assembled the data. Katsutoshi Hirose and Satoru Toyosawa contributed to the manuscript's writing. Katsutoshi Hirose and Kohei Kawamura reviewed clinical and radiological data.

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Data Availability The surgical samples and datasets analyzed in this study are available from the corresponding author upon request.

Code Availability Not applicable.

Declarations

Conflict of interest The authors declare no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The requirement for informed consent was waived by the Ethics Review Board of the Graduate School of Dentistry at the University of Osaka (nos. R5-E11 and R6-E24).

Consent to Participate This study has obtained IRB approval from the Ethics Review Board of the Graduate School of Dentistry at the University of Osaka, and the need for informed consent was waived.

Consent for Publication For this type of study consent for publication is not required.

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