Epithelial–myoepithelial carcinoma in the parotid gland with HRAS mutation: a case report

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest Statement

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Ethics approval and consent to participate

Study approval statement : This study protocol was reviewed and approved by the Ageo Central General Hospital Institutional Review Board

Patient consent statement

Informed consent has been obtained from all individuals included in this study.

Key words

salivary gland carcinoma, epithelial-myoepithelial carcinoma, HRAS mutation

Introduction

Epithelial–myoepithelial carcinoma (EMC) is a rare salivary gland neoplasm with an incidence of <1% among all salivary gland tumors.[1] EMC has a biphasic appearance with ductal epithelial and myoepithelial cells and a wide spectrum of histological appearances; therefore, it is often difficult to diagnose. *HRAS*mutations are a frequent genetic alteration in EMC[2]; however, few published reports have used the detection of *HRAS*mutations for diagnostic purposes. Herein, we describe two cases of EMC in which genetic testing revealed an *HRAS* mutation.

Case History

Patient 1

An 83-year-old woman presented with painless swelling in her right parotid gland without facial paralysis. Neck contrast-enhanced computed tomography (CT) showed a primary parotid tumor (24 × 19 × 16 mm in size) and no cervical metastases. Fluorine-18 fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET) showed abnormally high FDG uptake in the right parotid gland. Superior parotidectomy was performed without capsule rupture and with free margins; the pathologic stage was pT2N0M0. Pathologically, the tumor was multinodular with biphasic tubules and solid nests (Fig. 1a). Immunostaining showed positivity for cytokeratin (CK) AE1/AE3 in ductal epithelial cells and for SMA and p63 in myoepithelial-like cells (Fig. 1b, c). The Ki-67 labeling index (LI) was approximately 12%. Sanger sequencing revealed the *HRAS* Q61R mutation. Thus, the patient was diagnosed with EMC. One-year follow-up revealed no local recurrence or metastasis.

Patient 2

A 64-year-old man was referred for right parotid swelling with facial palsy (75/100: Sunnybrook method). Magnetic resonance imaging (MRI) showed a mass (45 × 30 × 26 mm in size) in the right parotid gland with suspected infiltration of the surrounding soft tissue and mandible. Parotid carcinoma stage cT4aN0M0 was diagnosed, and extended parotidectomy, ipsilateral selective neck dissection, facial nerve reconstruction, and anterolateral thigh flap reconstruction were performed. Histopathology of the resected tumor showed a salivary gland carcinoma with biphasic appearance composed mainly of basaloid cells with marked atypia (Fig. 2a). Immunostaining showed positivity for CK AE1/AE3, CK7, p40, DOG1, and p63 (Fig. 2b, c). S-100 protein, α-smooth muscle actin, vimentin, androgen receptor, HER2, CD56, chromogranin, synaptophysin, and β-catenin were negatively stained. The Ki-67 LI was approximately 70% in neoplastic cells. The differential diagnosis included basal cell adenoma (BCA)/basal cell adenocarcinoma (BCAC) and adenoid cystic carcinoma (ACC). Sanger sequencing revealed the*HRAS* Q61K mutation (no mutation in *HRAS* codons 12 and 13)**.** Thus, the final diagnosis was EMC. Since histopathology showed a high-grade carcinoma, we suspected EMC with high-grade transformation. The postoperative course was uneventful. The patient was disease-free at the 24-month follow-up.

Discussion

EMC has many histologic variations, thereby rendering an accurate diagnosis difficult.[2] Immunohistochemical staining is of limited value in differentiating EMC from other salivary gland tumors with biphasic differentiation; however, *HRAS* mutation testing may increase the rate of accurate diagnosis.

HRAS mutations are present in 81.7% of EMCs; however, no*HRAS* mutations have been identified in EMC-like salivary gland tumors, such as ACC, pleomorphic adenoma, BCA/BCAC, and myoepithelial carcinoma.[2] Herein, both cases lacked characteristic features of EMC, but the presence of *HRAS* mutations led to a diagnosis. Additionally, we could distinguish EMC from its histologic mimic more accurately by confirming the absence of β-catenin nuclear reactivity observed in BCA/BCAC and the lack of *MYB* mutations, which

indicate ACC. Notably, there is no significant correlation between the *HRAS* mutation status and histologic indicators of tumor aggressiveness.[2]

EMC is generally low-grade; however, 'high-grade transformations (HGTs)' have been reported.[1, 3] Dedifferentiation of salivary gland tumors has been described as HGTs, where a low-grade carcinoma results in a secondary high-grade carcinoma, which is associated with a worse prognosis. In case 2, a high degree of necrosis, numerous mitoses, and a high Ki-67 LI were seen, indicating that it was a high-grade tumor. It was difficult to conclude that it was an HGT of EMC based on the histopathological features; however, the *HRAS* mutation led to the diagnosis of EMC.

The standard treatment for EMC is complete surgical resection. The prognosis is relatively good in patients who have undergone wide surgical resection with clear margins.[4]

Conclusion

Genetic analysis for *HRAS* mutations is a crucial adjunct to pathological diagnosis of EMC and may play a decisive role, especially in difficult-to-diagnose cases.

Authors' Contributions

Taisei Yasuda : concept/design, analysis of patient data, drafting and revision of the manuscript, final approval of the manuscript

Masami Osaki : analysis of patient data, drafting and revision of the manuscript, final approval of the manuscript

Masahiko Sugitani : analysis of patient data, drafting and revision of the manuscript, final approval of the manuscript

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Figure Legends

Figure 1 a Carcinoma cells are found to be biphasic, ductal, and myoepithelial cells (H&E staining; 100× magnification). b Luminal cells are positive for CK (AE1/AE3) (Cytokeratin (AE1/AE3) immunostaining; 100x magnification) with (c) strong nuclear p63 staining (p63 immunohistochemistry; 100× magnification).

Figure 2 a Epithelial cell proliferation with partial glandular duct formation (H&E staining; 10× magnification). b Luminal cells are positive for CK (AE1/AE3) (Cytokeratin AE1/AE3 immunostaining; 10× magnification) with (c) intense staining for p63 (p63 immunohistochemistry; 10× magnification).