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Original Article

CTNNB1 mutations in basal cell adenoma of the salivary gland

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Background/Purpose: Basal cell adenoma (BCA) and basal cell adenocarcinoma (BCAC) are uncommon salivary gland tumors comprising proliferation of basaloid cells. Nuclear β-catenin expression and mutations in its encoding gene (*CTNNB1*) are reported to be specific to BCA. *PIK3CA* mutations are only found in BCAC not in BCA. However, in previous studies the number of cases was relatively small. The present study analyzed 44 cases of basal cell neoplasms to identify the *CTNNB1* and *PIK3CA* mutation profiles in this rare salivary gland tumor.
Methods: The basic clinical features and detailed histological patterns of 41 BCA and three BCAC cases were analyzed. All basal cell neoplasms and a tissue microarray of adenoid cystic carcinoma (AdCC) were tested for β-catenin immunohistochemistry. *CTNNB1*, *PIK3CA*, and *CYLD* mutations were detected by PCR and Sanger sequencing in each case.
Results: Nuclear β-catenin expression was present in 97.6% of BCA and 66.7% of BCAC cases but not in AdCC cases. *CTNNB1* mutations were found in 60% of BCA but not in BCAC. None of the tested cases had *PIK3CA* mutations. *CTNNB1* mutation trended to be more common in those cases having a predominant tubular or tubulotrabecular patterns ($p = 0.059$).
Conclusions: β-catenin immunohistochemistry is very useful for the differential diagnosis between BCA/BCAC and AdCC. *CTNNB1* mutations are common in BCA, especially those with tubular or tubulotrabecular patterns.

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Introduction

Basal cell adenoma (BCA) and basal cell adenocarcinoma (BCAC) are uncommon salivary gland tumors comprising the proliferation of basaloid cells without myxochondroid matrix.[1] BCA comprises 1–3% of salivary gland tumors and two-thirds of cases are female patients.[1–3] The most common location of BCA is the parotid gland. BCA can also occur in the submandibular gland or minor salivary glands in the upper aerodigestive tract.[1–3] BCAC is encountered less frequently compared with BCA. BCAC is morphologically similar to BCA, but is associated with invasion of the adjacent salivary parenchyma or extraparenchymal extension involving soft tissue, including fat and muscle.[4–6] Microscopically, basal cell neoplasms typically comprise two cell types: smaller cells with basaloid features, usually at the periphery of the tumor nests; and larger cells with more cytoplasm and vesicular nuclei, typically seen in the interior or forming ductal lumina. Several different architectural patterns can be observed in basal cell neoplasms, including tubular, trabecular, membranous, solid, and cribriform patterns.[1–3] Membranous BCA is characterized by puzzle-like nests of basaloid cells, surrounded by eosinophilic hyaline material, and has been termed as a dermal analog tumor of the salivary gland because of its similarity to dermal cylindroma.[2,3]

Nuclear β-catenin (encoded by *CTNNB1*) expression was reported to be present in BCA and in 2011, Kawahara et al. first reported a subset of BCA cases harboring *CTNNB1* gene mutations.[7,8] Nuclear β-catenin expression is a common finding in BCA and can also be observed in BCAC, but not in other types of salivary gland tumors.[6,8] β-catenin immunohistochemical staining is a useful test in the differential diagnosis between basal cell neoplasms and adenoid cystic carcinoma (AdCC).[6,8]

Although BCAC shares many pathological features with BCA (including nuclear expression of β-catenin), *CTNNB1* mutations have not been identified in BCAC.[9,10] Using the OncoPanel assay, Yo et al. found more complex and heterogeneous genomic changes in BCAC, including activating mutations in *PIK3CA* (encoding phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha), biallelic inactivation of *NFKBIA* (encoding nuclear factor-Kappa-B inhibitor alpha), and focal deletions of *CYLD* (encoding CYLD lysine 63 deubiquitinase).[9] *CYLD* gene mutations were identified in familial cylindromatosis and multiple familial trichoepithelioma (both now considered as part of the disease spectrum of Brooke-Spiegler syndrome).[2,11,12] Membranous BCA is associated with Brooke-Spiegler syndrome and *CYLD* gene mutations are also found in sporadic membranous BCA.[2,13,14]

The most important shortcomings of previous studies were the small number of cases (mostly comprising 10–20 cases).[6–10] In the present study, we first evaluated the clinicopathological features of 44 basal cell neoplasms. The expression of β-catenin in basal cell neoplasms was evaluated using immunohistochemistry. Analyses of *CTNNB1* and *PIK3CA* mutations were performed, and those without detectable mutations were selected for a *CYLD* mutation test. Furthermore, we compared the clinicopathological features of basal cell neoplasms with different mutations. We found that *CTNNB1* mutations were common in BCA, and trended to be associated with those cases that had predominantly tubular or tubulotrabecular patterns.

Materials and methods

Case selection

We searched the archives of the Department of Pathology at the National Taiwan University Hospital and identified 46 cases with an original diagnosis of BCA and three BCAC cases that were surgically resected between 2000 and 2017. All cases had available formalin-fixed and paraffin-embedded specimens. The clinical information for each patient, including age, gender, tumor location, tumor size, lymph node status, and local recurrence or distant metastasis during clinical follow-up, was collected from their medical records. Hematoxylin and eosin-stained slides were reviewed by two pathologists (Y.H.L. and M.S.H.), and the major histological patterns [including tubular/tubulotrabecular (Fig. 1), trabecular (Fig. 2A), cribriform (Fig. 2B), and solid (Fig. 2C and D)] observed under a low power objective at 10× magnification in each case were recorded. The tubular pattern was defined as the presence of well-formed tubular structures (Fig. 1A and B), or trabeculae with secondary dilated glandular structures filled with eosinophilic secretions or mucinous material, and the trabecular structure was distorted by these dilated ducts, as observed under a low power field (Fig. 1C). Basal cell neoplasms composed of pure tubular patterns are extremely rare, and most cases have mixed tubular and trabecular patterns; therefore, cases with mixed tubular and trabecular patterns (each component comprising at least 25% of the tumor) were classified as having a tubulotrabecular pattern (Fig. 1D). The trabecular pattern was defined as trabeculae without ductal spaces, or in which the small ductal spaces in the trabeculae could only be appreciated properly under a high power field and the trabecular structure was still preserved under a low power field. We believe that well-formed tubules and dilated ductal spaces filled with eosinophilic or mucinous secretion represent well-differentiated features, and basal cell neoplasms could be further categorized into two groups as tubular and non-tubular types. The tubular types included those with a predominantly tubular/tubulotrabecular or cribriform pattern (>50% of the tumor); the non-tubular types included those with a predominant trabecular or solid pattern (>50% of the tumor). There was no membranous-predominant BCA case in this cohort.

Five cases originally diagnosed as BCA were excluded and reclassified as myoepithelioma (four cases) and epithelial–myoepithelial carcinoma (one case). Forty-one BCA and three BCAC cases were selected for further analysis. A tissue microarray containing 37 cases with an original diagnosis of AdCC was used to compare the β-catenin levels between basal cell neoplasms and AdCC. This study was approved by the Research Ethics Committee of the National Taiwan University Hospital (201702078RINA).

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