Human Pathology (2018) 73, 59–65

ELSEVIER

Human PATHOLOGY

www.elsevier.com/locate/humpath

Original contribution

BRAF and *KRAS* mutations in tubular apocrine adenoma and papillary eccrine adenoma of the skin☆,☆☆

Jau-Yu Liau MD[a,b,*], Jia-Huei Tsai MD[a,b], Wen-Chang Huang MD[c], Jui Lan MD[d], Jin-Bon Hong MD[e], Chang-Tsu Yuan MD[a]

[a]*Department of Pathology, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei 10051, Taiwan*
[b]*Graduate Institute of Pathology, National Taiwan University College of Medicine, Taipei 10051, Taiwan*
[c]*Department of Pathology, Wan Fang Hospital, Taipei Medical University, Taipei 11696, Taiwan*
[d]*Department of Pathology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung 83301, Taiwan*
[e]*Department of Dermatology, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei 10002, Taiwan*

Received 26 September 2017; revised 17 November 2017; accepted 1 December 2017

Keywords:
Tubular apocrine adenoma;
Papillary eccrine adenoma;
RAS;
BRAF;
Syringocystadenoma papilliferum

Summary Tubular apocrine adenoma (TAA) and papillary eccrine adenoma (PEA) are benign sweat gland tumors. Their names imply that they exhibit apocrine and eccrine differentiation, respectively. However, morphologically they are very similar and are often indistinguishable. The molecular pathogenesis of either tumor is poorly understood at present. On the basis of an index case of nipple adenoma that was morphologically reminiscent of cutaneous TAA/PEA and harbored a $BRAF^{V600E}$ mutation, we investigated whether a similar genetic change is also present in TAA/PEA. *BRAF*, *RAS*, and *PIK3CA* mutation analyses, and $BRAF^{V600E}$-specific immunohistochemistry were performed for 24 TAAs/PEAs, 10 eccrine poromas, 7 apocrine cystadenomas, 2 TAA-like adenomas associated with nevus sebaceus, and one apocrine adenoma probably arising in anogenital mammary-like glands (AGMLGs). The results demonstrated that $BRAF^{V600E}$ mutations were present in TAAs (9/15, 60%) and PEAs (7/9, 78%), but not in other neoplasms. Two additional TAAs harbored $KRAS^{G12D}$ mutations. In addition, a $KRAS^{G12C}$ mutation was identified in one nevus sebaceus-associated TAA-like adenoma. The speculated AGMLG-related apocrine adenoma had a $PIK3CA^{H1047R}$ mutation. We concluded that activating *BRAF* and *KRAS* mutations were commonly present in TAAs/PEAs, indicating that in addition to a morphological resemblance, they are closely related genetically. Therefore, they could be considered to be united as a single entity. By contrast, the apocrine adenoma probably arising in AGMLG harbored a *PIK3CA* mutation, which is also commonly present in hidradenoma papilliferum. Further studies are necessary to determine whether the pathogenesis of AGMLG-related tumors is similar to breast tumors.

1. Introduction

Tubular apocrine adenoma (TAA) and papillary eccrine adenoma (PEA) are benign sweat gland tumors purportedly exhibiting apocrine and eccrine differentiation, respectively.

☆ Competing interests: The authors declare no conflict of interest.
☆☆ Funding/support: Grant No.: NTUH 106-N03 (to Jau-Yu Liau).
* Corresponding author at: Department of Pathology, National Taiwan University Hospital, No 7, Chung-Shan South Road, Taipei 10051, Taiwan.
E-mail address: 019188@ntuh.gov.tw (J. -Y. Liau).

https://doi.org/10.1016/j.humpath.2017.12.002
0046-8177/

Histologically, both are circumscribed tumors composed of tubular glands in the dermis, sometimes with subcutaneous extension. [1,2]. The glands are lined by cuboidal luminal epithelial cells, which have eosinophilic cytoplasm and round or ovoid nuclei with small nucleoli. A layer of myoepithelial cells is also present around the luminal cells. Intraluminal papillary or micropapillary growth is frequently seen. The stroma is often sclerotic with a mild mononuclear cell infiltrate. Decapitation secretion, the histological evidence of apocrine differentiation, is present in TAA, but by definition, is absent in PEA. Some tumors are associated with a syringocystadenoma papilliferum (SCAP) [3]. Because SCAP is usually regarded as an apocrine neoplasm, SCAP-associated tumors tend to be classified as TAAs. TAAs are most commonly seen in the head and neck region, especially the scalp, whereas PEAs are more common in the extremities. Nevertheless, they are often indistinguishable by routine histological examinations. In fact, decapitation secretion has been observed in eccrine glands [4], and hybrid adnexal tumors exhibiting both lines of differentiation have also been reported [5,6]. Some authors have suggested that they are part of the spectrum and have proposed to use unifying terms such as tubulopapillary hidradenoma, papillary tubular adenoma, or simply, tubular adenoma, to encompass both entities [6,7].

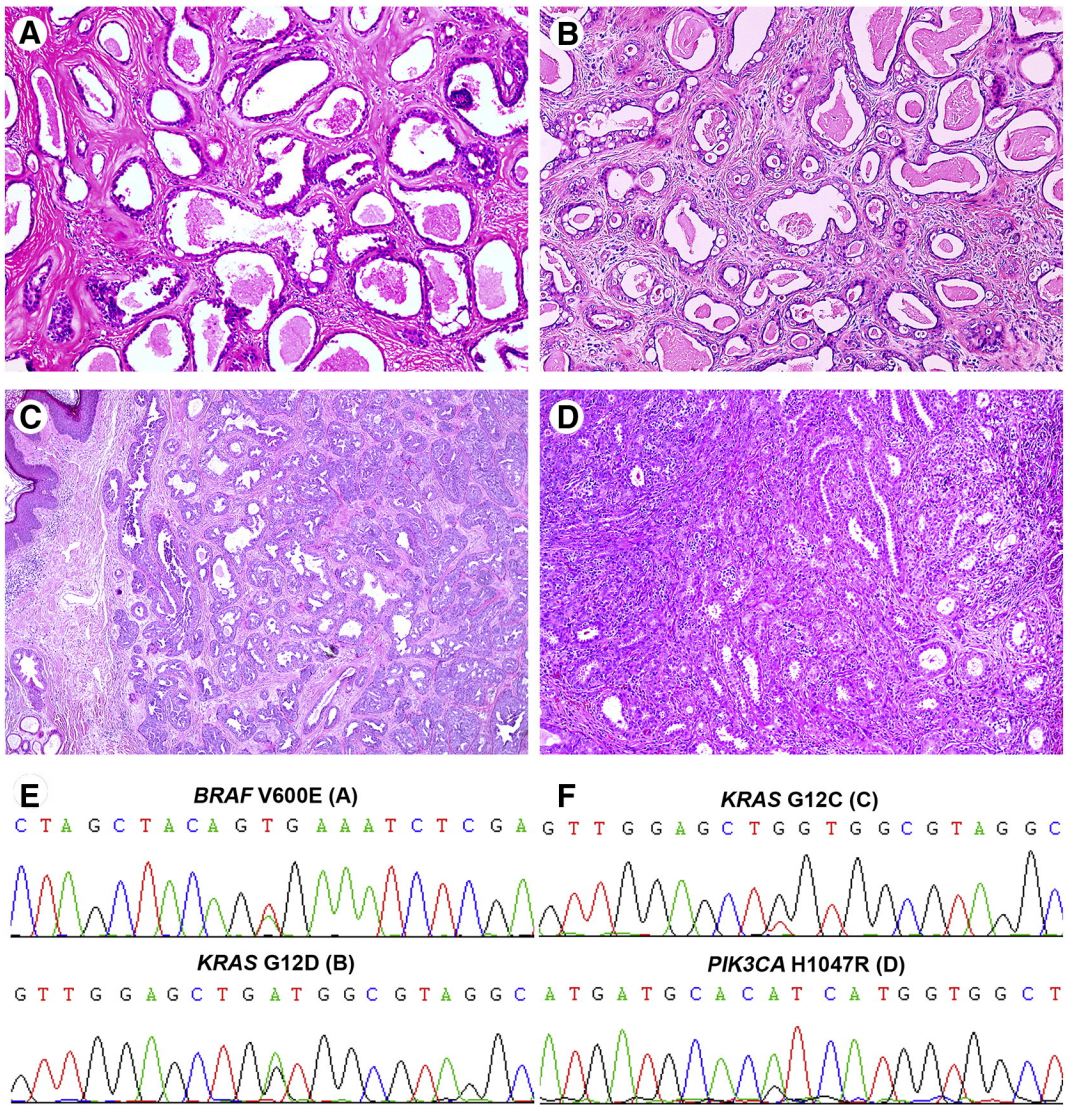

Fig. 1 Representative histological images and sequencing chromatograms of the adenomas in this study. A, A TAA with a *BRAF*^{V600E} mutation. Its sequencing chromatogram is shown in the top of panel E. B, A TAA with a *KRAS*^{G12D} mutation. Its sequencing chromatogram is shown in the bottom of panel E. C, A TAA-like adenoma with a *KRAS*^{G12C} mutation arising in association with a NS. This case exhibited more prominent epithelial proliferation than a usual TAA. Note the papillomatous epidermal hyperplasia and dilated apocrine glands with epithelial cell hyperplasia in adjacent skin. Its sequencing chromatogram is shown in the top of panel F. D, The apocrine adenoma with a *PIK3CA*^{H1047R} mutation probably arising in AGMLG. Note the conspicuous decapitation secretion. Its sequencing chromatogram is shown in the bottom of panel F. A-D, Hematoxylin and eosin stain; original magnification: A, B, and D, ×100; C, ×40.