Acral BRAF-mutated tubular adenoma should be distinguished from HPV42-related digital papillary adenocarcinoma

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NOTES AND COMMENTS

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We read the article entitled "Two distinct pathogenic pathways of digital papillary adenocarcinoma – *BRAF* mutation or low-risk HPV infection," which was recently published in your journal, and would like to share our thoughts on the findings to avoid confusion in skin tumor nomenclature and prevent potential harm to patients from misdiagnosis.

Digital papillary adenocarcinoma (DPA) is a rare sweat gland carcinoma capable of metastasis. It almost exclusively arises at acral sites.[1,2] Microscopically, DPA is characterized by a mixed solid and cystic architecture with, often focal, papillary projections (Figure 1). Tubular structures sometimes forming "back-to-back glands" are associated with a myoepithelial component present at the periphery but also forming solid nests. Cytologic features are often low grade, but they do not predict clinical behavior.[3] Rare DPA cases with anaplastic cytology have been reported.[4,5] Immunohistochemistry usually reveals diffuse SOX10 positivity, EMA, and CEA expression restricted to the glands while p63 expression is observed in the myoepithelial component[6] (Figure 1).

The diagnosis of DPA can be challenging. It primarily needs to be distinguished from benign sweat gland tumors arising at acral sites, such as hidradenoma,[7] cystadenoma,[8] or tubular adenoma.[9,10] Tubular adenoma is characterized by multiple independent tubules, lined by a luminal layer of cuboidal cells sometimes harboring decapitation secretion associated with a peripheral myoepithelial component. Frequent pseudopapillary structures are detected in this setting and should not lead to misdiagnosis of these cases as DPA.[11]

Molecular analyses of sweat gland tumors have identified recurrent and mutually exclusive oncogenic drivers such as *CRTC1/3::MAML2* in hidradenoma and their malignant counterparts[12] or *BRAF* mutations in tubular adenoma.[13] Recently, human papillomavirus 42 (HPV42) was discovered in DPA.[5,14–17] Indeed, DPA genome was found in 96%–100% of tested DPA tumors,[5,16] but not in any other sweat gland neoplasm or adenocarcinoma.[5]

In their article, Bui et al[18] reported a series of eight acral sweat glands tumors diagnosed as "DPA." In contrast to prior observations with a larger set of tumors[5,14,16] they claim to have identified two "DPA" groups with distinct phenotypes, genetics, and outcomes. "Group A" ($n = 4$) included painless slow-growing nodules microscopically characterized by small, well defined dermal tumors forming independent glandular structures. Such glands were composed of cuboidal luminal cells with pseudopapillary projections associated with a myoepithelial cells layer at the periphery. Only slight cytologic atypia and rare mitotic figures were observed while no cellular necrosis, perineural or vascular invasion were detected. No recurrence or metastasis were observed. Molecular analysis revealed *BRAF* mutations in all analyzed samples while no HPV genome was detected.

In contrast, "Group B" included fast-growing tumors with aggressive behavior including one tumor with local recurrences, lymph nodes, and lung metastases. These cases displayed a more solid architecture and several extended into subcutaneous tissue. Mitotic figures and cytological atypia were reported. In situ hybridization targeting so called "low grade" HPV genotypes including HPV42 was positive in all cases and *BRAF* mutation was absent.

In our opinion, the tumors of the group A had the microscopic and genetic hallmarks of tubular adenoma without any worrisome clinical or microscopic characteristics, while only Group B cases had morphologic, immunohistochemical and genetic features of DPA.

Unfortunately, there are confusing published data suggesting a gray zone/progression between tubular adenoma and DPA.[18–20] We believe that there is a clear distinction between these two tumors, which is crucial for surgical management and assessment of recurrence risk. DPA is a cancer with metastatic potential,[1,3] while tubular adenoma is a benign neoplasm.[21] The concept of "papillary adenocarcinoma in situ" was introduced several years ago for tubular adenoma cases harboring atypical microscopic features including sclerotic stroma, mitotic figures and/or foci of necrosis.[11,20] However, no solid clinical or pathologic evidence of malignant transformation was provided in the reported cases, including reference 40 cited by Bui et al.[22] Therefore, it is hard to justify why such cases should be regarded as carcinoma. When a tumor meets microscopic and molecular criteria for a tubular adenoma, it should be classified as such irrespective of the anatomic site where it occurs. We apply the same principle for the diagnosis of acral hidradenomas or poromas. When such benign tumors affect acral sites, they should not be classified as DPA. These benign tumors are cured by conservative excision, while the standard of care for patients with DPA is usually amputation and sentinel lymph node biopsy.[23]

We acknowledge that it can be difficult to render a definitive distinction between a tubular adenoma and DPA on histopathologic grounds alone, especially on a partial incomplete biopsy sample. However, the identification of distinct and mutually exclusive oncogenic drivers, that is, HPV42 and *BRAF* mutations in DPA and tubular adenoma, respectively, has greatly facilitated their diagnostic distinction.

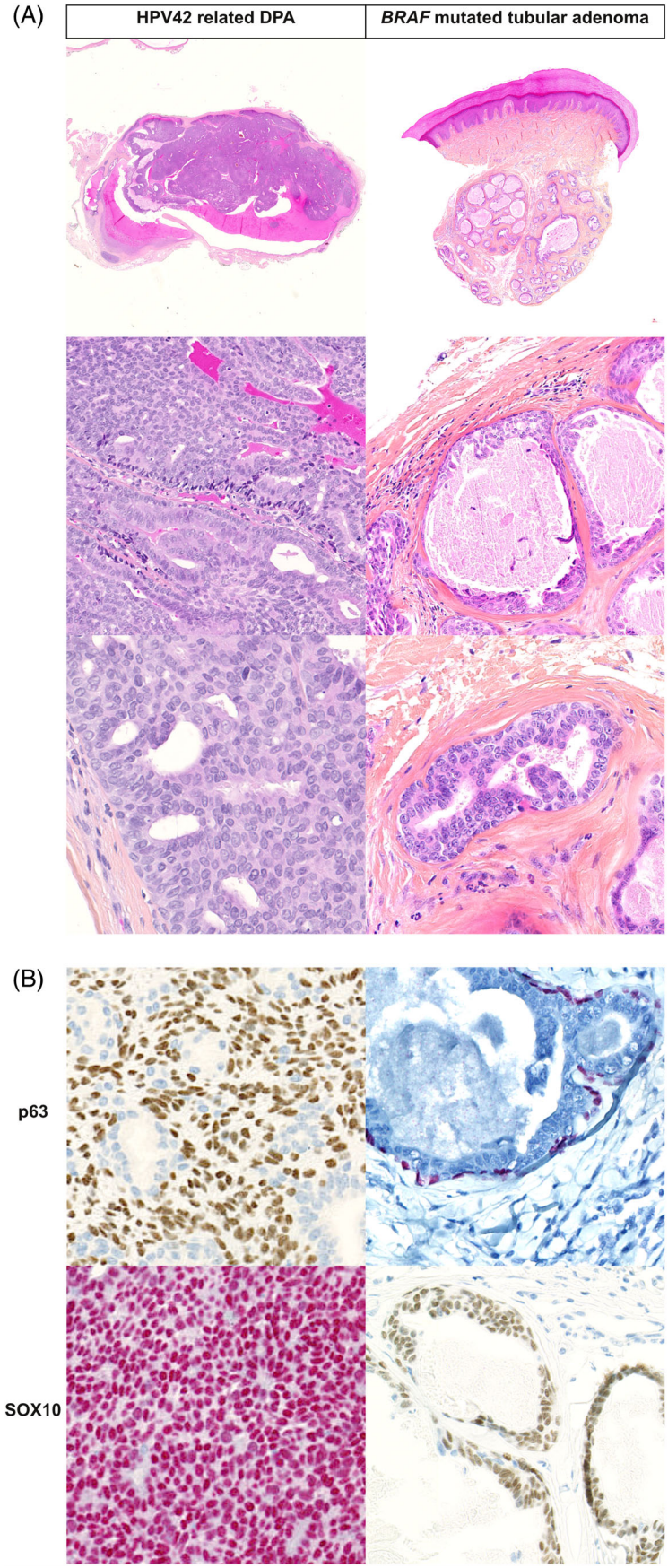

FIGURE 1 Morphological and immunohistochemical features of HPV42-related digital papillary adenocarcinoma (DPA) and *BRAF*V600E mutated tubular adenoma. (A) Microscopic features of the cases. DPA harbors a mixed solid and cystic architecture with focal papillary projections (×1, HPS). "Back-to-back" glands are frequently observed in this setting (×10 and ×20, HPS). By contrast, tubular adenoma is composed of independent tubules with frequent pseudopapillary formation (×4, HPS). Sclerotic stroma and decapitation secretion are observed (×10 and ×20, HPS). (B) Immunohistochemical features. DPA and tubular adenoma exhibit similar immunohistochemical profiles with diffuse SOX10 positivity, and p63 expression restricted to the myoepithelial component (×20).

Although there are two previous publications that reported *BRAF*V600E mutations in "DPA,"[19,24] both had microscopic features most in keeping with a tubular adenoma, occurred in women (DPA usually affects men) and none of them was located on a digit.

In summary, we believe that HPV42-related DPA and *BRAF*-mutated tubular adenoma constitute two separate tumor entities with distinct morphology, genetic, and behaviors. Tubular adenomas can occur at acral sites, and it is important not to confuse them with DPA for best patient care.

KEYWORDS

BRAF, digital papillary adenocarcinoma, HPV42, tubular adenoma

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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