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Is aggressive digital papillary adenocarcinoma (ADPA) really aggressive? Does it only occur at digital location? Does it always have microscopic papillary features? Is it really adenocarcinoma? Let's us address these questions one by one.

Is ADPA aggressive? From the term, namely, aggressive digital papillary adenocarcinoma, one would interpret this as high grade malignant tumor with grim prognosis. Is this the case? Let's answer this question with historical literature review. In 1979 Helwig from the Armed Force Institute of Pathology introduced a term called aggressive digital papillary adenoma and presented 22 cases under this term at the American Academy of Clinical and Pathologic Conference in Chicago [1]. A brief written description of these cases was found as differential diagnosis in an article entitled "eccrine acrospiroma" published in 1984 [2]. Helwig described the so-called aggressive digital papillary adenoma by these words:

> "I presented 22 examples of aggressive digital papillary adenoma of which 21 occurred on the digits and one on the sole… Microscopically, nests and masses of cuboidal to columnar cells irregularly infiltrate the collagenous stroma. Usually, pleomorphism is minimal. The epithelial patterns vary from solid foci to a more common picture of repeated acinar or gland-like structures fused into larger masses. The gland-like structures have minute or, occasionally, large lumens and often show a papillary configuration. Small foci of squamous differentiation may occur. Thirteen of the 22 tumors recurred at least once, some extended into subjacent bone and, occasionally, amputation of the digit was required. Two tumors metastasized, one to the lung." [2]

As one can see from what was described, these lesions, some of them with recurrences and even metastasis, were not adenomas but carcinomas. For reasons unknown, Helwig did not make straightforward diagnosis of these lesions as carcinoma even in the presence of metastasis, instead he called them "aggressive" adenoma. The term "aggressive" adenoma was used here by Helwig to describe a lesion considered by him as an adenoma but showing recurrences and metastasis. In other word, if this lesion was called carcinoma, then the word "*aggressive*" would be redundant, since recurrence and metastasis are expected for carcinomas. Decades later when these lesions were called rightly by Duke et al. (also from Armed Force Institute of Pathology) as carcinomas, namely, aggressive digital papillary adenocarcinoma [3], the word "aggressive" was not removed and it remained in the term up to today. With the word "aggressive" remaining in the term, it gives a wrong impression that the lesion under consideration

is a high-grade carcinoma. As a matter of fact, the lesion under consideration is not high-grade carcinoma. Even Duke et al. acknowledged that the lesions under discussion were low-grade malignant tumor [3]. In order to avoid confusion, we agree with Suchak et al. who proposed to remove the word "aggressive" from the term aggressive digital papillary adenocarcinoma [4].

Does ADPA only occur at digital location? Although most if not all cases reported in the literature were from digital or nondigital acral skin, there is no reason to believe that this kind of lesion only occurs on digits or is restricted to acral skin. This kind of lesion must have occurred at skin sites other than acral location and is simply called something other than ADPA. The predominant digital location of those lesions documented in the literature was most likely due to selection bias. Most, if not all, cases reported in the few large series were referring cases. Lesions on digits are often difficult to excise completely without digital amputation, thus, it has a tendency to recur and calls for pathology consultation. Furthermore, Duke et al. did acknowledge that this kind of lesion might arise elsewhere other than acral location [3]. Recently an example of such case was reported in thigh [5].

Does ADPA always have microscopic papillary features? According to Duke et al., the typical ADPA is "multinodular, solid, and cystic with papillary projections present in the cystic spaces… Twelve (18%) of the neoplasms were essentially only solid, lacking cystic spaces. Characteristic of all lesions was a pattern of fused back-to-back glands lined by cuboidal to low columnar epithelial cells in the solid portion of the tumors" [3]. As one can see, papillary features are not present in all cases of ADPA. In contrast, solid component is a constant feature present in all cases of ADPA. In this sense, it is better to call ADPA solid adenocarcinoma rather than papillary adenocarcinoma. In our opinion, there is no need to include the word "papillary" in the term since some ADPA may not have papillary feature at all. If one likes, he or she can simply call adenocarcinoma with solid and papillary features or adenocarcinoma with multinodular growth pattern.

Is ADPA really adenocarcinoma? Following the reports from the Armed Force Institute of Pathology, a few articles, mostly single case reports, under the term of ADPA, were published by other authors [6-22]. Many of these authors appeared to be confused and included different lesions under the term of ADPA. For example, in 2006 Crowson et al. illustrated a case (figures 15 and 16 in the article) under the term ADPA and commented that histopathologically the lesion was "cognate to that of ductal carcinoma in situ of the breast" [21]. From the photomicrographs illustrated there, it appears that an intact peripheral myoepithelial cell layer was present, so we believe the case is actually adenocarcinoma in situ. In 2010 Hsu et al. described an 8 mm nodule on the finger of a 28-year-old woman and diagnosed as aggressive digital papillary adenocarcinoma [22]. According to the authors, the lesion was excised with positive margin, and there was no evidence of disease progression at the six-year follow-up. The photomicrographs of H&E and P63 stain provided by the authors for their case (figures 2 and 3 in the article) showed clearly the presence of an intact myoepithelial cell layer. This led us to conclude that the lesion actually represented so-called papillary eccrine adenoma, which is a type of adenocarcinoma in situ in our opinion [23,24].

Among the articles from Armed Force Institute of Pathology, only Kao et al. mentioned the presence of myoepithelial cells in an abstract published in 1984 [25]. Kao et al. described the myoepithelial cells in these words: "as in other eccrine tumors, three main cells types were identified, namely, clear and dark epithelial cells bordering on the tubular and ductal lumina and a third myoepithelial type forming the outer layer." Interestingly in subsequent full articles published in 1987 [26] and 2000 [3], the authors did not comment on whether the lesion under discussion had any myoepithelial component or not. In an article published in 2012, Suchak et al. collected 31 cases from referral archives at three institutions and reported under the term of ADPA [4]. Besides the series of cases from the Armed Force Institute of Pathology, this report represented the only study with a large series of cases. By using immunocytochemical staining Suchak et al. demonstrated the presence of myoepithelial cells in ADPA. According to Suchak et al. immunocytochemical staining was done in 8 out of 31 cases and the authors stated that:

> "The presence of SMA-positive and calponin-positive myoepithelial cells around glandular structures has been thought of as a feature of benignity in the context of cutaneous adnexal tumors. Five of 6 cases in this study showed positivity for SMA in the outer myoepithelial layer (diffuse in 3, focal in 2), whereas all 6 cases were strongly positive for calponin. This, however, was not predictive of outcome: 1 of these cases had multiple recurrences eventuating in pulmonary metastases (with diffuse SMA staining of myoepithelial cells throughout the tumor, illustrated in Fig. 3), 2 cases had no adverse outcomes, and 2 were lost to follow-up. One case that was SMA negative had no adverse outcome 20 months after complete excision of the tumor. The presence of tumor associated myoepithelial cells should not be construed as an indication of benignity but rather another indication for a primary adnexal tumor should metastasis be a clinical or diagnostic consideration." [4]

If what Suchak et al. stated here is true, then ADPA might not be adenocarcinoma but adenomyoepithelial tumor. In general, the presence of both epithelial and myoepithelial

cells in a neoplasm indicates that the neoplasm under consideration is either benign or carcinoma in situ or adenomyoepithelial tumor. In our opinion, those cases reported by Suchak et al. with the presence of both epithelial and myoepithelial cells are adenomyoepithelial tumors (either adenomyoepithelioma or adenomyoepithelial carcinoma). The case Suchak et al. described (case #29) with multiple recurrences and later on pulmonary metastasis is clearly adenomyoepithelial carcinoma (also called malignant adenomyoepithelioma). According to Suchak et al., the patient was 16 years old female who presented with a lesion in her big toe, which was excised with unknown marginal status. Microscopically the lesion was that of multilobular predominantly solid tumor with tubules and focal cystic and papillary changes. Mitotic rate was stated to be 6.5/mm^2. Immunohistochemical staining was done and clearly showed the presence of both epithelial and myoepithelial cells (Figure 3 in the article). The patient had multiple local recurrences and metastasis to leg and lung over 21 years of follow up. This case, in our opinion, both clinically and histopathologically is undoubtedly that of adenomyoepithelial carcinoma.

In summary, the so-called aggressive digital papillary adenocarcinoma is not an aggressive tumor. There is no reason to believe that it is restricted to digital location. It does not always have microscopic papillary feature and furthermore it might be adenomyoepithelial tumor rather than adenocarcinoma. Thus, the so-called aggressive digital papillary adenocarcinoma, in our opinion, is not really *aggressive digital papillary adenocarcinoma*.

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