

## **A case of intracystic apocrine papillary tumor: a concern for histopathologic evaluation of malignancy**

Running title: Intracystic apocrine papillary tumor

**Key words:** intraductal papillary carcinoma, breast, apocrine papillary tumor, high molecular weight cytokeratin, myoepithelial cell

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**Abstract**

Intraductal/intracystic papillary carcinoma (IPC) of the breast is defined as a malignant non-invasive papillary tumor arising from the ductal-lobular system. Based on the presence of myoepithelial cells in the cystic wall, IPC is distinguished from encapsulated papillary carcinoma (EPC). Here, we report a case of an intracystic apocrine papillary tumor in the breast of a 49-year-old woman. Histopathologic examination revealed that the entire papillary structures and cyst wall were comprised of apocrine cells, some of which showed nuclear atypia with macronucleoli. Immunohistochemical examination revealed a lack of myoepithelial cells in the papillary fronds and cyst wall. Although the dense proliferation of apocrine cells mimicked a cribriform pattern, detailed examination identified a delicately intermingled interstitium in the cribriform-like growth area in the present case. Only a few apocrine variants of IPC or EPC have been reported to be malignant or potentially malignant. Since even benign apocrine lesions are known to lack myoepithelial cells, histopathologic evaluation regarding malignant potential requires caution in apocrine variants.

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## Introduction

Intracystic/intraductal papillary carcinoma (IPC) of the breast is defined as a malignant non-invasive neoplastic epithelial proliferation with a papillary architecture in the lumen of the ductal-lobular system in the WHO classification published in 2012 [4]. Histologically, the tumor shows slender fronds with absent or scant myoepithelial cells and epithelial cells, which all have architectural and cytological features of ductal carcinoma in situ [4]. Encapsulated papillary carcinoma (EPC) is a variant of papillary carcinoma, which is surrounded by a thick fibrous capsule. IPC has myoepithelial cells in the cyst wall and is clearly distinguished from EPC.

A few cases of apocrine variants of IPC or EPC have been reported to date [2,3,7]. Owing to the limited cases with short-term follow-up periods, their malignant potential has been inconclusive. Furthermore, histologic evaluation of malignancy is potentially difficult, particularly in low-grade tumors, because even non-neoplastic apocrine lesions may lack myoepithelial cells [2,8].

Here, we describe a case of an intracystic atypical apocrine papillary tumor simulating IPC, but with complete absence of myoepithelial cells in the cyst wall, and discuss the current issues regarding the malignant potential of IPC and/or EPC.

## Case report

A 49-year-old woman was referred to our hospital after an abnormality was detected on a mammographic examination. Sonography showed a cystic mass measuring 2 cm in the subareolar region of her left breast. Two weeks later, the mass had enlarged to 7×4×4 cm in size, and contained some subcentimetric mural nodules. Suspecting breast cancer, a surgical excision of the mass was performed.

## **Pathological findings**

Grossly, the translucent cyst had a smooth inner surface and included three papillary yellow nodules measuring 1.0, 0.9, and 0.3 cm in diameter, respectively.

Cytologically, the cyst contents included some three-dimensional papillary clusters in a background of scattered foamy macrophages (Fig. 1A). The cells of these clusters had relatively rich cytoplasm, large nuclei, and prominent macronucleoli. On the other hand, some clusters also included cells with abundant and granular cytoplasm, which were identical to benign apocrine cells (Fig. 1B). The cells were generally cohesive and the borders of the cell membranes were distinct. These findings suggested intracystic apocrine neoplasia, but were inconclusive for malignancy.

Histologically, epithelial papillary lesions were present in the cystically dilated duct (Fig. 2A). Branching fibrovascular stalks were relatively broad with occasional edematous areas, and were covered by cells with abundant eosinophilic granular to pale cytoplasm (Fig. 2B). No myoepithelial cells were found. The nuclei were prominent with distinctive nucleoli (Fig. 2C). Although cribriform-like patterns were observed focally (Fig. 2D and E), more detailed examination revealed the presence of a delicate interstitium between glands (Fig. 2E). We confirmed that each gland was surrounded by type IV collagen immunohistochemically (Fig. 2F). Mitotic figures were sparsely observed (Fig. 2G). The cyst wall was covered with atrophic apocrine epithelium (Fig. 2H).

In an immunohistochemical study, the tumor cells showed diffuse and strong cytoplasmic positivity for 15-kDa glycoprotein of gross cystic disease (GCDFP-15). Myoepithelial markers such as p63 (Fig. 2I), calponin, and CD10 were negative in both

the papillary nodules and cyst wall. High molecular weight cytokeratins (HMWCs) such as CK5/6 (Fig. 2J) and 34 $\beta$ E12 were also negative in the nodules. Androgen receptor was entirely positive (Fig. 2K), while estrogen receptor, progesterone receptor, and Her-2 were completely negative. Proliferative activity measured with Ki-67 was less than 1%.

## Discussion

An intracystic/intraductal papillary tumor composed of an entirely apocrine epithelium is rare. Seal et al. [7] reported five cases with this lesion as encapsulated apocrine papillary carcinoma for the first time. According to their descriptions, all of their cases showed varied complexity of apocrine cell proliferation and had pseudopapillary and/or cribriform architectures. The cytological atypia were also varied in their cases. They described that it was not yet known whether this lesion is a form of papillary hyperplasia of apocrine cells or a true neoplasm [7].

Laforga et al. [3] reported a case with an apocrine type of EPC, and described that their case showed features fitting with low-grade carcinoma according to the criteria of O'Malley and Bane [6], such as cell size, atypical nuclei with macronucleoli, architecture showing papillary and cribriform patterns of growth, and so on.

Cserni [2] reported a case of intracystic papillary apocrine proliferation. He mentioned the difficulty associated with determination of malignancy because of the short-term follow-up, but supported benign biologic behavior.

One of the most challenging issues is to assess apocrine atypia, and mainly differentiate between atypical apocrine proliferations and low-grade apocrine ductal carcinoma in situ (DCIS). O'Malley et al. [6] summarized the criteria that have been

proposed thus far. Atypical apocrine lesions show three-fold nuclear enlargement with nucleolar enlargement, slightly irregular nuclear membranes, and fine chromatin. Nuclear stratification or tufting of the epithelium may be present in atypical apocrine lesions. Low-grade DCIS shows irregular nuclear membranes and coarse chromatin, and may exhibit a characteristic cribriform architecture. However, there are no broadly accepted criteria for distinguishing these lesions to date.

For the differentiation, it may be difficult to use elements such as irregular nuclear membranes or coarse chromatin because a “borderline” apocrine lesion shows “borderline” nuclear atypia. These nuclear findings are relatively vague and noncommittal, especially for cases in which pathologists are irresolute. Among the criteria summarized by O’Malley et al. [6], the cribriform architecture might be a relatively identifiable feature because of its distinct pattern.

In the present case, the apocrine papillary epithelium revealed relatively uniform nuclei with nucleolar enlargement, smooth nuclear membranes, and fine chromatin. Architecturally, an indistinct cribriform pattern was seen in part of the lesion. Coincident with this area, some atypical features such as rough chromatin and increased nuclear-cytoplasmic ratio were discernible. These findings might suggest malignant potential for this lesion. At first sight, this area appeared to be a “true” cribriform pattern with punched-out regular spaces. However, as a result of more detailed observations, an interstitium intervened delicately among the glands and there was no solid growth pattern. We therefore judged it not to be a “true” cribriform architecture, but a tubular architecture.

Although a lack of myoepithelial markers is commonly used as a hallmark for papillary carcinoma, it has reported that apocrine lesions, either benign or malignant,

can show reduction and occasional complete loss of myoepithelial cells [1,8]. Tramm et al. [8] described that a malignant diagnosis with apocrine changes of the breast cannot yet solely rely on the presence or absence of myoepithelial cells, and should be based on the overall morphology, i.e., the cytologic and architectural features.

HMWCs such as 34 $\beta$ E12 and CK5/6 are widely used for distinguishing benign proliferative lesions from DCIS, since the former characteristically show a mosaic pattern and the latter is negative for these antigens [5]. However, these antibodies are often useless for apocrine proliferative lesions because an apocrine metaplastic epithelium is included within “false-negative” groups [5]. These peculiar immunohistochemical panels of the apocrine epithelium make the diagnosis of “borderline” lesions more difficult. The present case also showed complete negativity for myoepithelial markers and HMWCs.

In summary, an intracystic papillary tumor composed of an entirely apocrine epithelium is rare. Although its monotonous appearance and florid growth might confuse pathologists, there are no distinct criteria to distinguish an atypical apocrine lesion from low-grade apocrine DCIS to date. Moreover, immunohistochemical panels such as myoepithelial markers and HMWCs may not be helpful for the diagnosis of this lesion. An apocrine epithelium has a broad cytoplasm and therefore its relatively dense proliferation mimics solid growth or a cribriform architecture. Consequently, pathologists should be cautious in the evaluation of malignancy for apocrine variants of IPC or EPC.

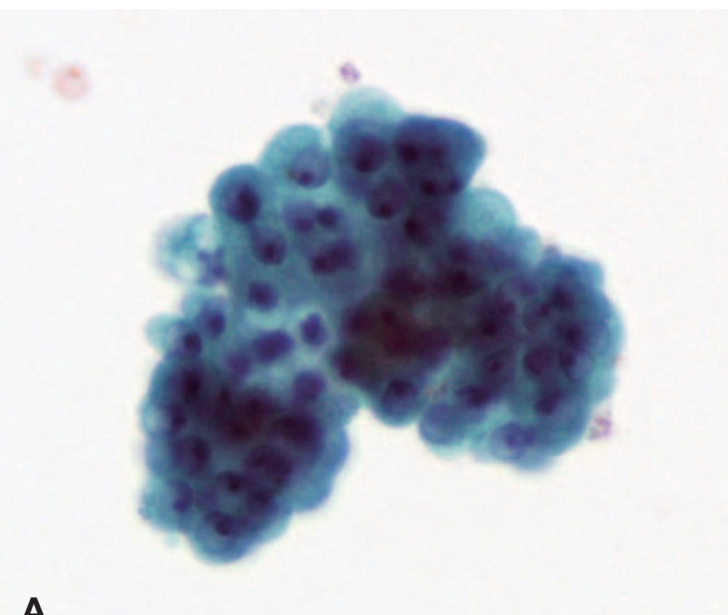
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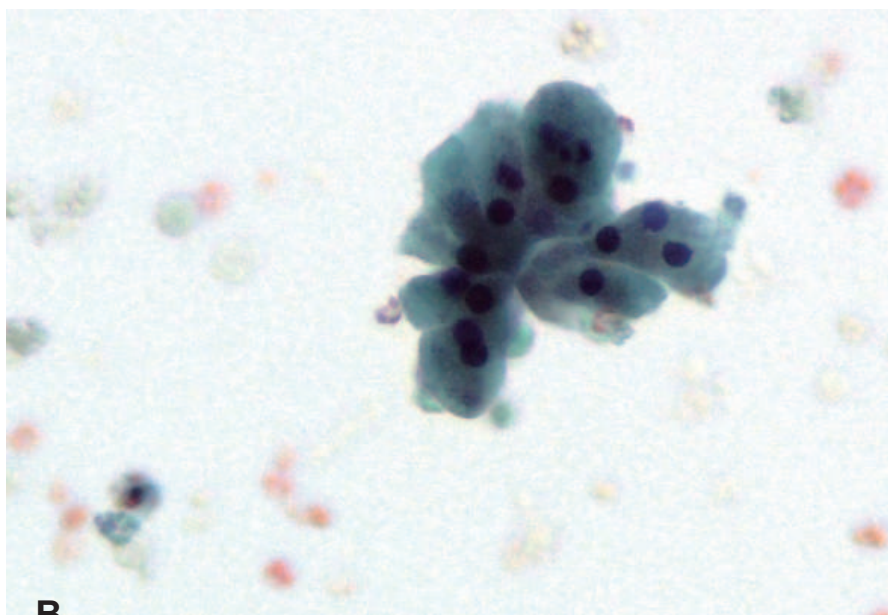
### Figure legends

**Fig. 1** Cytology of the contents of the cyst (Papanicolaou 400×): (A) Three-dimensional papillary cluster of cells with relatively rich cytoplasm, large nuclei, and prominent macronucleoli. (B) Some clusters had a sheet-like appearance, and were composed of obvious benign apocrine cells with abundant and granular cytoplasm.

**Fig. 2** Histological features: (A) Papillary nodule in a cystically dilated duct (H&E 20×). (B) Papillary architecture with an edematous stalk lined by apocrine cells (H&E 200×). (C) Relatively monotonous cells with abundant, eosinophilic, and granular cytoplasm (H&E 400×). (D) Focal cribriform-like architecture (H&E 100×). (E) High magnification of a cribriform-like portion showing a tubular pattern with intervention of a delicate interstitium (H&E 400×). (F) Type IV collagen surrounded each gland (400×). (G) Scattered mitoses were discernible (H&E 400×). (H) Atrophic apocrine cells lined the cyst wall (H&E 400×). (I) Both papillary nodules and the cyst wall had no cells positive for p63 (100×). (J) Proliferative cells were entirely negative for CK5/6 (100×). (K) Strong and diffuse immunoreactivity for androgen receptor (200×).

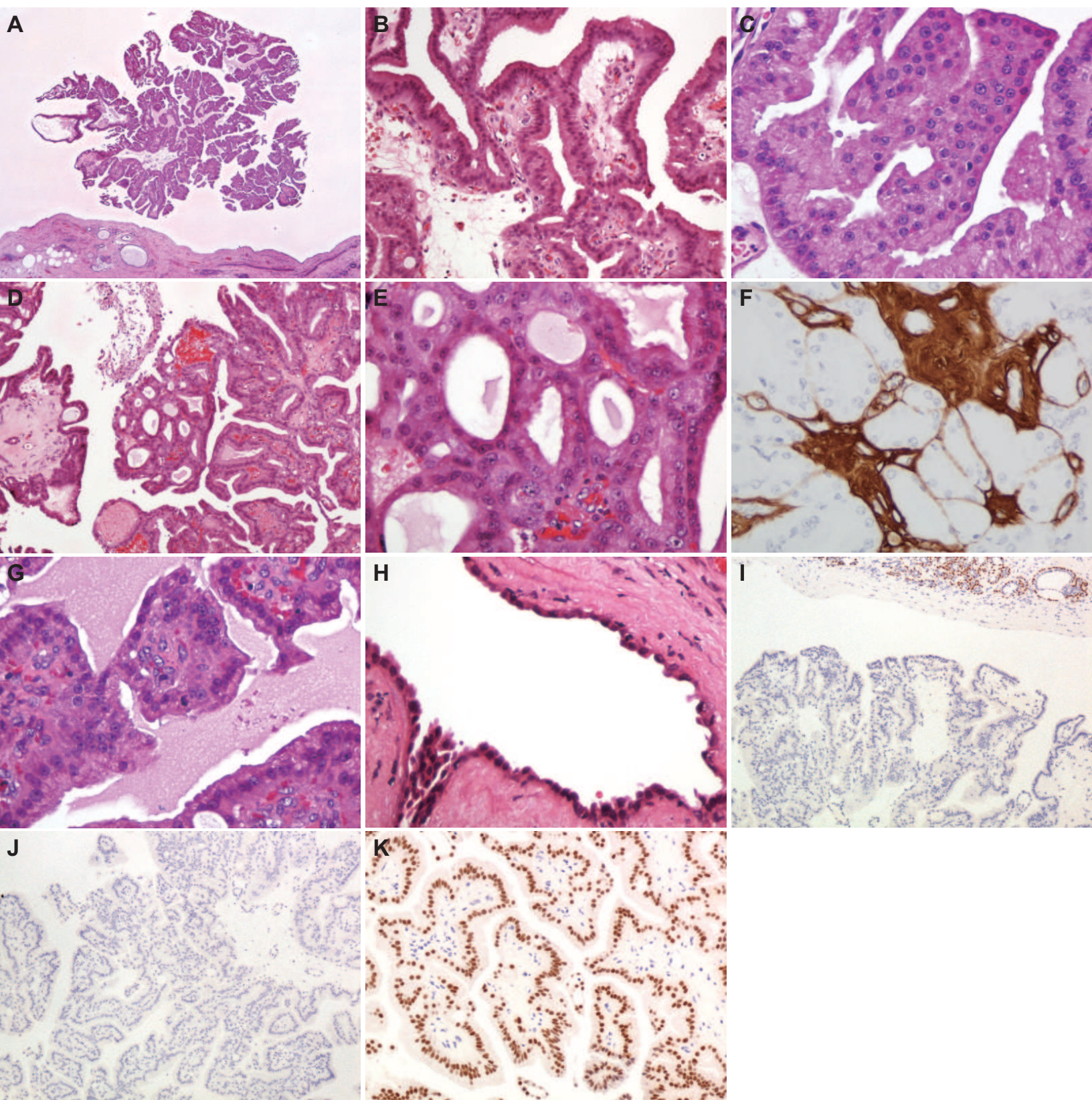


A



B

Fig. 1



**Fig. 2**