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□ Case Report □

Adenomyoepithelioma of the Breast

-Its Diagnostic Problems and Histogenesis-

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We report three cases of adenomyoepithelioma of the breast that occurred in middle aged women. The tumor is characterized by a balanced proliferation of epithelial tubules and surrounding myoepithelial cells that are spindle shaped or have clear cytoplasms. The first case mimicked tubular adenoma in the initial biopsy. However, on excision it turned out to be an adenomyoepithelioma of the tubular type. The other two cases were lobulated types and had fibroadenomatous areas. The morphologic appearance of this tumor varies, making it misleading to other benign or even malignant lesions. The tumor has a potential for local recurrence, therefore, wide excision is recommended for proper diagnosis and treatment.

Key Words: Adenomyoepithelioma, breast, adenoma, adenosis

Myoepithelial cells are an integral part of the normal histology of the mammary glands. Hyperplasia of the myoepithelial cells have been well recognized in sclerosing adenosis. However, lesions with striking overgrowth of myoepithelial cells are rare. Myoepithelial lesions of the breast are divided into three categories: myoepitheliosis, adenomyoepithelioma, and myoepithelial carcinoma(Tavassoli, 1991). Adenomyoepithelioma is a rare benign breast tumor in which the dual proliferation of epithelial and myoepithelial cells is characteristic. Since Hamperl's first report(Hamperl, 1970), there were only two large series of breast adenomyoepitheliomas with collective review (Rosen, 1987; Tavassoli, 1991). Most of the reported cases were in females but one male case was also reported(Tamura *et al.* 1993). Although the majority of myoepithelial tumors are benign, some of them can recur and rarely metastasize(Loose *et al.* 1992). Failure to recognize this tumor may lead to an inappropriate diagnosis such as fibroadenoma, sclerosing adenosis, tubular adenoma, and even as a malignancy. We report three cases of adenomyoepithelioma and for further accurate diagnosis, propose its possible histogenesis.

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CASE REPORT

Case 1: A 50-year old woman was presented with a 2 year history of a mass in her left breast. Physical examination revealed a 2×1.5 cm-sized ovoid mass in the inferior medial part of the left breast without palpable axillary lymph nodes. It was a mobile, painless mass with firm consistency. Mammography showed a 0.7 cm sized lobulated and well circumscribed mass without microcalcifications. Initial biopsy showed proliferation of small regular tubules surrounded by clear cells, making the diagnosis of tubular adenoma. Simple excision of the mass was done without axillary dissection.

Case 2: A 30-year old female was presented with a palpable mass in the left upper medial breast. It was 1.5×1.5 cm in size and movable on palpation. Mammography showed a well circumscribed, lobulated mass with multiple microcalcifications, partly surrounded by a thin capsule. Excision was performed under the clinical impression of fibroadenoma.

Case 3: A 35-year old female was presented with a lobulated movable mass in the subareolar area of left breast. Mammography showed a 1.7×1.5 cm sized well circumscribed round mass suggesting a benign nature. Intraoperative frozen biopsy diagnosis was fibroadenoma. Complete excision was performed.

Pathologic Findings

Case 1: Excised breast showed a pale pinkish gray, well-circumscribed, and lobulated mass(2×1.5 cm). A cleft was formed at the periphery. The tumor was composed of a diffuse proliferation of epithelial and myoepithelial cells. Epithelial cells were arranged in abortive or round patent tubules and ectatic spaces(Fig. 1A). Epithelial cells lining the round tubules were cuboidal and monotonous with vesicular nuclear chromatin and prominent nucleolus. Epithelial sheets were composed of polygonal cells with abundant pale pinkish cytoplasm. Medium sized and ectatic tubules were filled with pinkish or pale gray fluid. Occasional large ectatic tubules contained foamy cells. The lining epithelial cells of some tubules showed apocrine change(Fig. 1B). Mitotic figures were 1-2/10 HPF. These epithelial structures were surrounded by clear myoepithelial cells. Thick pink hyalinized stroma suggestive of basement membrane like material separated these epithelial-myoepithelial

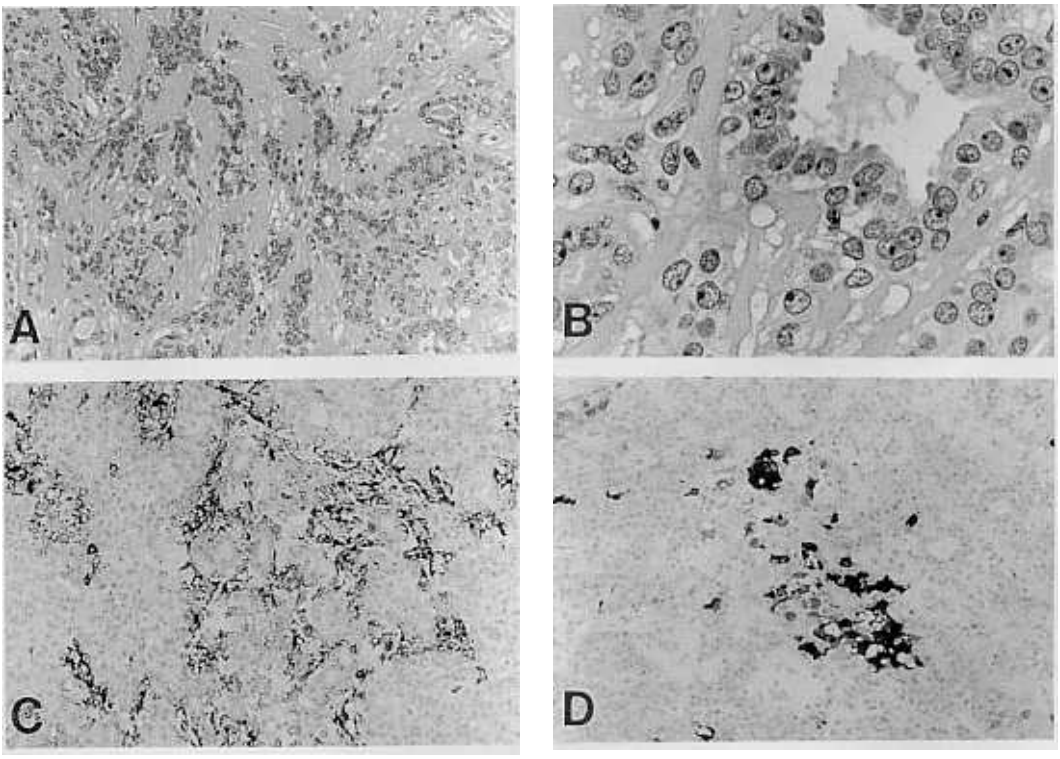

Fig. 1. ***A:*** *Round to oval epithelial tubules are surrounded by clear cells and thick hyalinized material.*
B: *Note apocrine change of lining epithelia.*
C: *Smooth muscle actin was diffuse positive in clear cells.*
D: *S-100 protein was focal positive in clear cells.*

nests. Spindled myoepithelial cells were not identified. Immunohistochemical study revealed that smooth muscle actin was diffuse positive(Fig. 1C) and S-100 protein was focal positive in the clear cells(Fig. 1D).

Case 2: A pinkish white well-circumscribed mass was 2×1 cm in size. Microscopically, the tumor had an expansile margin. Histological findings were variable from area to area, but the overall proportion between the epithelial and myoepithelial cells was equal. Tumor stroma was loose, myxoid, and densely collagenous. The epithelial cells formed either acini or long tubular structures in the loose connective tissue stroma which was quite similar to fibroadenoma(Fig. 2A). These epithelial nests were surrounded by scanty spindle cells. The cytoplasms showed foci of apocrine differentiation. The myoepithelial cells were mainly spindle shaped, forming fascicles in the collagenous stroma or thick cuffs around the small or collapsed tubules(Fig. 2B). Both epithelial and myoepithelial cells showed blend nuclei with inconspicuous nucleoli. Mitotic activity was less than 1/10HPF. Many calcific spherules were scattered in the dense collagenous area not described previously. Immunohistochemical stain for smooth muscle actin demonstrated diffuse strong positivity in the spindle cells(Fig. 2C), while S-100 protein showed weak positivity in some of the spindle cells (Fig. 2D)

Case 3: A well-circumscribed oval mass was 2×1.5 cm in size. Thick collagenous septae gave the mass a vague lobulation on low power view. One third of the mass had features similar to those of fibroadenoma with collapsed tubules surrounded by myxoid stro-

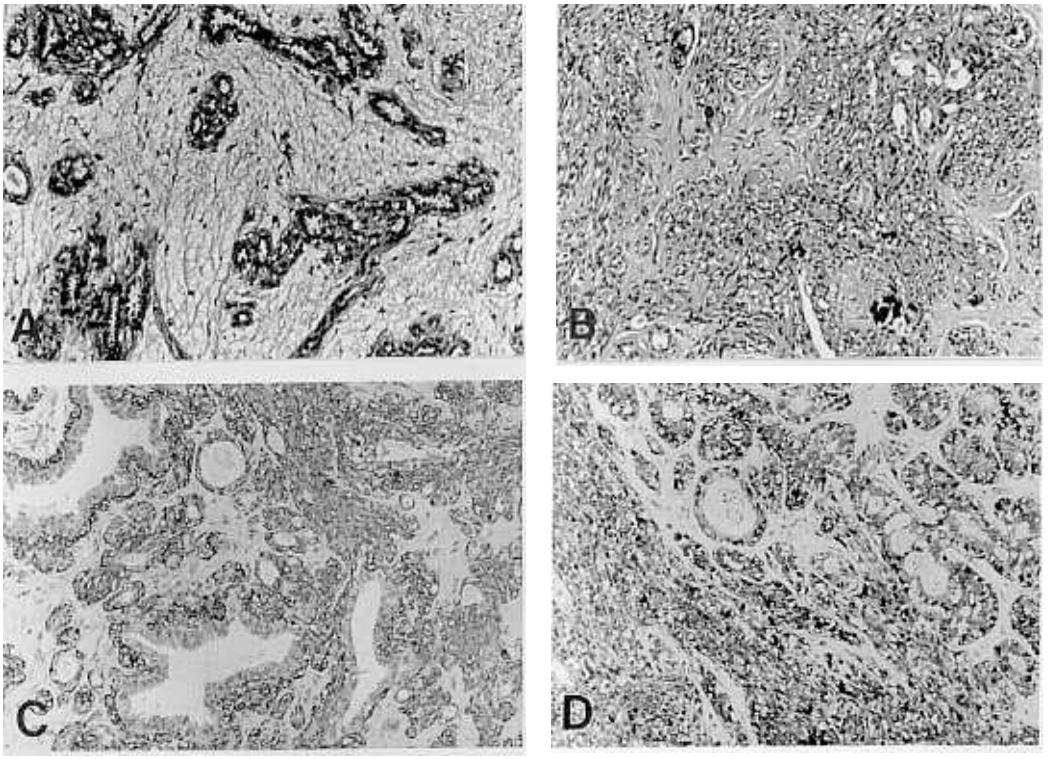

*Fig. 2. **A:** Irregular long ducts are in the loose myxoid stroma similar to fibroadenoma.*
__B:__ Spindle cells around collapsed epithelial tubules are forming lobulated figures. Many calcific spherules are conspicuous.
__C:__ Smooth muscle actin was diffusely positive in spindle cells around ducts.
__D:__ S-100 protein was positive in occasional spindle cells.

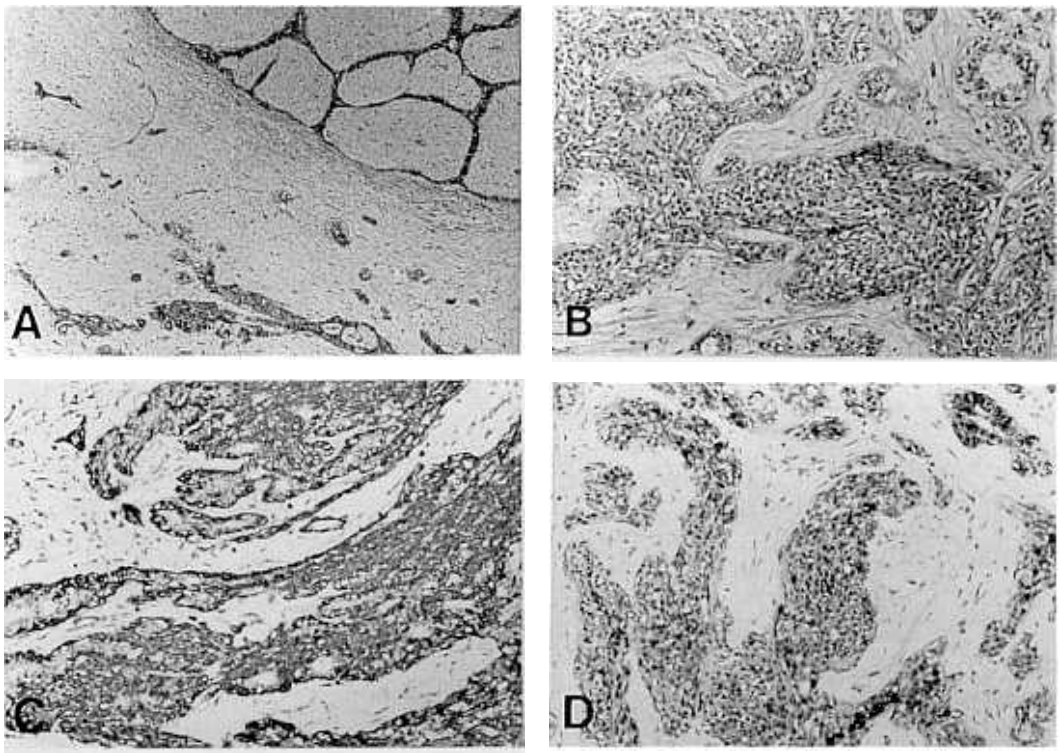

Fig. 3. A: Some portion shows fibroadenomatous areas.
B: Multinodular proliferations of spindle cells are compressing epithelial structures.
C: Smooth muscle actin was diffuse strong positive in spindle cells.
D: S-100 protein was positive in occasional spindle cells.

ma(Fig. 3A). The remaining portion showed micronodular spindle cell proliferations that cuffed collapsed epithelial tubules(Fig. 3B). Both epithelial and spindle cells had no cytologic atypia and less than 1 mitosis/10HPF. Smooth muscle actin showed diffuse and strong positivity in these spindle cell cuffs (Fig. 3C). But S-100 protein was more weakly positive than smooth muscle actin in the same cells(Fig. 3D).

DISCUSSION

Myoepithelial cells are normally present in the breast throughout the mammary duct system. Neoplasm of pure myoepithelial origin or mixed epithelial and myoepithelial origin are rather common in the salivary glands but are rare in other sites including the breast. The myoepithelial proliferative lesions of breast were classified as myoepitheliosis, adenomyoepithelioma, and malignant myoepithelioma(Tavassoli, 1991). The majority of adenomyoepitheliomas have been described as well circumscribed, firm lobulated masses with a size from 0.5 cm to 5.0 cm. Histologically they are composed of mixture of epithelial and myoepithelial cells. The adenomyoepithelioma was subdivided into the spindle cell, tubular, and lobulated types for benign tumors and carcinoma arising in adenomyoepithelioma (Tavassoli, 1991). The morphologic appearance of this tumor varied widely depending on the ratio of proliferating myoepithelial cells to glandular epithelial cells, on the configuration of the tumor cells, and on the degree of fibrosis. Due to such a varing degree of morphologic variation, this tumor should be differ-

entiated from adenosis, tubular adenoma, ductal adenoma, fibroadenoma, and myoepithelioma. Myoepithelioma is defined as a tumor composed entirely of myoepithelial cells with no identifiable epithelial cells. Considering most of the benign epithelial proliferative lesions accompany myoepithelial attendance, differentiation of adenomyoepithelioma from other benign epithelial lesions seems to be rather arbitrary and subjective. It is not infrequent to find adenomyoepitheliomatous hyperplasia in fibroadenoma, adenosis, and fibrocystic change(Kiaer *et al.* 1984; Eusebi *et al.* 1987). However, it is not clear how a large proportion of myoepithelial cells involved should be classified as adenomyoepithelioma. According to the previous descriptions, a balanced proliferation of epithelial and myoepithelial cells or myoepithelial overgrowth is required to be an adenomyoepithelioma(Hamperl, 1970). The myoepithelial differentiation can be confirmed by positive staining for S-100 protein and actin. It deserves to have notice that reactive, transformed, and neoplastic myoepithelial cells display various reactivity for S-100 protein(Mori *et al.* 1987). The first case had areas of intraductal proliferation, and the second and third cases had focal fibroqsadenomatous areas. We could discriminate these tumors by identifying the overall balanced or predominant myoepithelial proliferation in the excised specimens. It may be therefore impossible to diagnose adenomyoepithelioma in a small biopsy specimen. It is evenly unclear that a sharp distinction could be made between adenomyoepithelioma and adenomyoepitheliomatous hyperplasia in other benign lesions.

Histogenesis of this tumor is unclear at present. We propose that adenomyoepithelioma should be derived from myoepithelial overgrowth from long standing adenosis, fibroadenoma, and other benign breast lesions. Supporting evidences are as followings; Kiaer *et al.*(1984) reported adenomyoepithelial adenosis changed into an adenomyoepithelioma and eventually to low grade malignant adenomyoepithelioma in the course of 18 years. Adenomyoepithelial adenosis was similar in several ways to microglandular adenosis. And it is not infrequent to find myoepithelial proliferation in the background of fibroadenoma and fibrocystic disease(Kiaer *et al.* 1984; Eusebi *et al.* 1987). The present two cases had also reminiscent areas of fibroadenoma. The average age of the reported cases are older than that of fibroadenoma, adenosis, and fibrocystic change. Whether the margin of an adenomyoepithelioma is infiltrative or circumscribed may depend on its precursor lesion.

Even though the presence of the two cell component is considered as an evidence for benignity, the biologic behavior is still uncertain. Several local recurrences(Rosen, 1987; Young and Clement, 1988) and distant metastasis(Loose *et al.* 1992) have been reported. Histologic findings suggestive of malignancy include high mitotic activity and/or foci of cytologic malignancy(Zarbo and Oberman, 1983; Loose *et al.* 1992; Chen *et al.* 1994; Pauwels and Potter, 1994).

In conclusion, complete excision is necessary for the accurate diagnosis and treatment of this unusual breast lesion.

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