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Pleomorphic Adenoma of the Breast with Atypical Hyperplasia May Originate from Progenitor Cells: A Case Report and Review of the Literature

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Abbreviations:

PA: Pleomorphic Adenoma; SG: Salivary Gland; SGPA: Pleomorphic Adenoma of the Salivary Glands; WHO: World Health Organization; ADH: Atypical Ductal Hyperplasia; UDH: Usual Ductal Hyperplasia; AFIP: Air Force Information Program; DCIS: Ductal Carcinoma in Situ

1. Abstract

1.1. Aims: Pleomorphic adenoma (PA) of the breast in association with severe atypical hyperplasia is exceedingly rare, and supports the opinion that breast PA is not always benign. We report a case of breast PA with severe atypical hyperplasia of squamous epithelium and discuss its histological origin, morphological characteristics, and biological behavior. Methods and results: The tumor was comprised of nodules forming numerous expanding ducts. The histological components included squamous epithelium, myoepithelium, glandular epithelium, cartilage, and bone. There was atypical hyperplasia of the squamous epithelium, which was mixed with various components including papilloma, adenomyoepithelioma, and myoepithelioma. Immunohistochemical analysis revealed diffuse CK5/6 and CK14 positivity; CK7 positivity among clear-cytoplasmic cells and glandular epithelium; CK8/18 positivity in glandular epithelium; S-100 positivity in clear-cytoplasmic cells, spindle, and cartilage-like cells; CD10, p63, and calponin positivity in the myoepithelium of large ducts and isolated nodules; and 10% Ki67 positivity overall. HER2 and EGFR were negative, but there was 2+ ER and PR positivity in 80% of the glandular epithelium, and 30% p53 positivity overall. Immunofluorescence detected scattered CD44+/CD24- in the tumor. Conclusion: The presence of epithelial and mesenchymal components possibly originating from progenitor cells indicates that breast PA is a low-grade malignancy. When atypical hyperplasia of squamous epithelium is observed, the surgeon should obtain an adequate margin to avoid recurrence.

2. Introduction

Pleomorphic adenoma (PA) is the most common type of salivary gland (SG) tumor. It usually arises from the epithelium of large ducts and mesenchymal tissues and is found in the parotid gland,

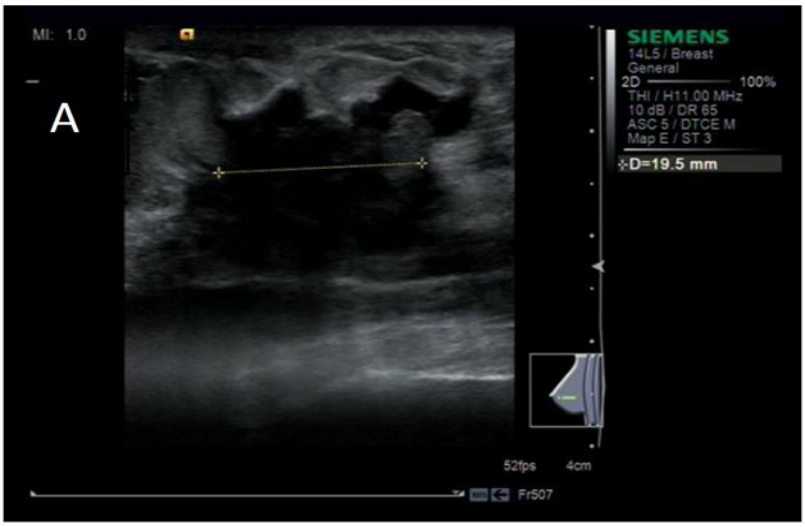
paranasal sinus, nasal septum, and palatoschisis [1]. PA sometimes originates from skin (chondroid syringoma), [2] and, very rarely, PA is observed in breast. The World Health Organization (WHO) classification of tumors of the breast (4th Edition) describes PA of the breast as morphologically similar to PA of the salivary glands (SGPA), and Eusebi and Foschini have described characteristic histological features including glands, nests, and single epithelial and myoepithelial cells immersed in myxochondroid stroma [3]. Rosen's breast pathology lists PA as one of a number of types of mixed tumors of the breast and notes the formation of a collagenized myxoid matrix that is frequently converted into cartilage, sometimes

with calcification and ossification, and marked by various proliferative patterns, including foci that resemble cellular mixed tumors of the salivary glands, areas with distinct papillary components, and areas of squamous and sebaceous epithelial metaplasia similar to the metaplastic changes that occur in conventional adenomyoepithelioma [4]. SGPA is known as a benign tumor, and favorable outcomes are commonly reported, but the histologic morphology of breast PA actually differs from that of SGPA, and, although the majority of reported cases of breast PA are also benign, the biological character of this tumor is not yet confirmed, and one other case of PA associated with atypical hyperplasia has reported [5]. In this report, we present a case of breast PA accompanied by severe atypical hyperplasia of the squamous epithelium and discuss the histologic origin, morphologic character, and biological behavior.

3. Case Presentation

A 63-year-old woman presented one week after discovering a lump in her left breast. On examination, there was a well-defined 2 cm x 2 cm painless mass with no swelling and no ulceration of the skin. The axillary lymph nodes were not palpable. The patient had no previous history of surgery or family history of hereditary diseases. No treatment has been given since the onset of illness. On ultrasound, the low-echo mass measured 1.95 cm x 1.83 cm and was located at 4 o'clock, 2.4 cm away from the nipple and was well-circumscribed with an abundant blood supply. It was diagnosed

as BI-RADS 4a (Figure 1). An excision frozen biopsy was performed. Macroscopic examination showed a soft cystic tumor measuring 3.2 cm x 1.8 cm x 1.5 cm enclosing a 1.5 cm x 1.0 cm x 1.0 cm nodule, one side of which was closed to cyst wall. The cut surface of the nodule was grey-white in color with a fragile chondral appearance, and the other cyst walls were rough and soft (Figure 2). Microscopically, the tumor was constructed of nodules forming numerous expanding ducts; large ducts became cystic; ductal epithelial cells of cystic wall proliferated; partial squamous cells went to metaplasia, acini were observed, and stroma proliferated to form nodules. There were multiple components including cartilage, mucinous stroma, scattered or flake-like spindle cells floating in stroma, clear-cytoplasmic epithelioid cells, squamous epithelium, and glandular epithelium. The epithelial cells were intertwined and the partial squamous cells had high nuclear/cytoplasmic (N/C) ratios and showed irregular, hyperchromatic eosinophilic nuclei with thickened nuclear membranes and frequent mitoses (about 5/10 HPF in the most active fields), but no pathologic mitoses. These findings are characteristic of severe atypical hyperplasia of the squamous epithelium. Besides the cystic tumor, there were two solid nodules. One of them was enveloped by fibrous tissue and contained epithelium, cartilage, and bone components. Adenomyoepithelioma was found at the fibrous envelope and there were compressed myoepithelial cells around the nodule. The other nodule showed papillary hyperplasia of the glandular epithelium with atypical ductal hyperplasia (ADH). A mucous matrix was observed in the stroma and there was normal breast tissue adjacent to the mucous matrix. The tissue surrounding the tumor showed usual ductal hyperplasia (UDH) (Figures 3 and 4). The frozen biopsy diagnosis was intraductal papilloma accompanying squamous epithelial metaplasia and hyperplasia and cartilage and bone metaplasia of stroma. An extended tumor resection was performed and the excised



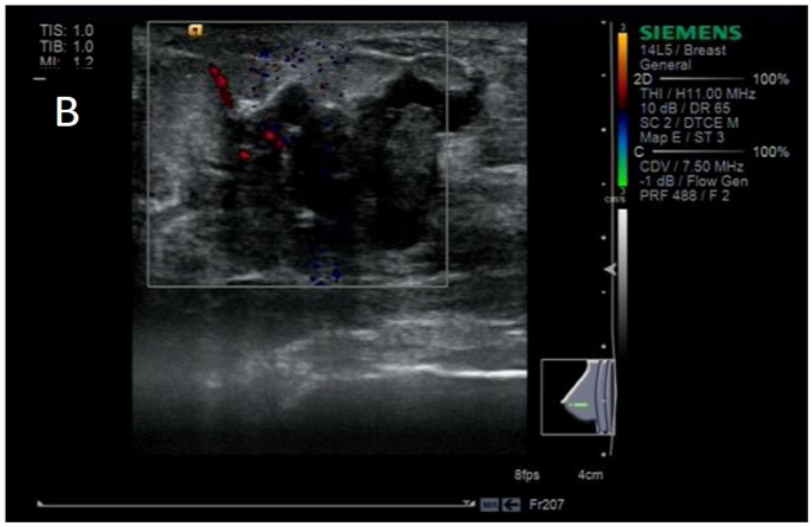


Figure 1: **A.** The low-echo mass measured 1.95 cm x 1.83 cm and was located at 4 o'clock, 2.4 cm away from the nipple; **B.** Internal echo was not homogeneous, but it had rich blood supply, expansive ducts and conneted with each other.

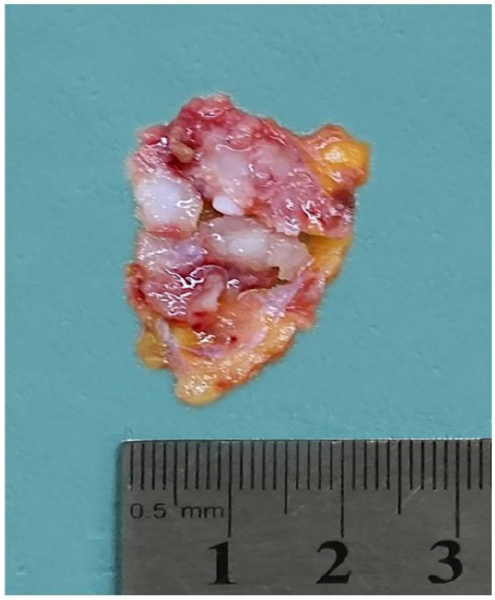


Figure 2: Macroscopical examination showed soft cystic tumor. The nodule in the cyst measured 1.5 cm × 1.0 cm × 1.0 cm. Cut surface of the nodule showed grey-white color with fragile chondral looking.

tumor was sent for permanent pathology and immunohistochemical examination, which showed CD10, p63, and calponin positivity in the large ducts and myoepithelium outside the nodule, but not in the cells adjacent to the adipose tissue. There was also CD10, p63, and calponin positivity in isolated myoepithelium in the tumor. There was diffuse CK5/6 and CK14 positivity in squamous epithelium, partial glandular epithelium, and some clear-cytoplasmic cells in the mucous matrix, and p63 was positive in the myoepithelium around ductal and differentiated-squamous epithelium. CK7 was positive in clear-cytoplasmic cells and glandular epithelium. CK8/18 was positive in glandular epithelium. Ki67 was positive in 10% of the tumor cells. HER2 was negative (Figure 5). There was 2+ positivity for ER and PR in 80% of the glandular epithelium. All of the tumor cells were negative for EGFR, and 30% were positive for p53. Clear-cytoplasmic cells and spindle and cartilage-like cells were S-100+ (data not shown). Notably, the immunofluorescence assay detected scattered CD44+/CD24- tumor cells, accounting for about 5% of the tumor cells (Figure 6). The tumor had clear margins and myoepithelium around the ducts. Although the myoepithelium was lacking locally in one of the nodules, the tumor did not invade the adipose tissue. We described this as an unobvious invasive growth pattern. On the other hand, there was severe atypical hyperplasia of squamous epithelium with active but not pathologic mitoses and low Ki67. The final pathology diagnosis was breast PA with severe atypical hyperplasia of squamous epithelium. The patient recovered well and there was no recurrence during follow-up for 12 months.

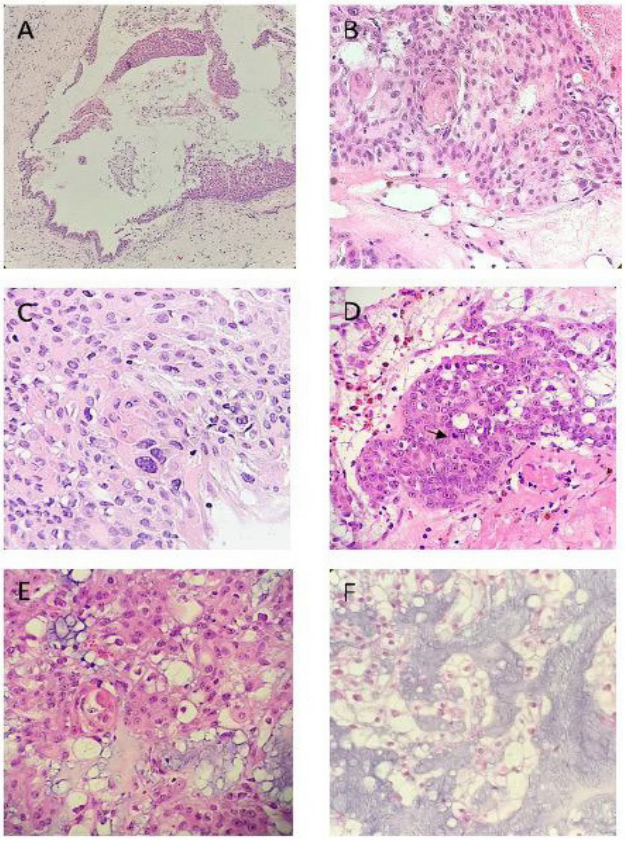


Figure 3: A. Large ducts became cystic expand, ductal epithelial cells of cystic wall proliferated. × 40; **B.** Ductal epithelium presented squamous metaplasia with severe atypical ductal hyperplasia × 200; **C.** ADH. × 400. **D.** Mitosis (Arrow showed); **E.** Acres of epithelial cells floated in mucous matrix, some cells presented keratinization, some cells showed clear-cytoplasm. × 400; **F.** Clearcytoplasmic cells floated in mucous cartilage stroma ×400.

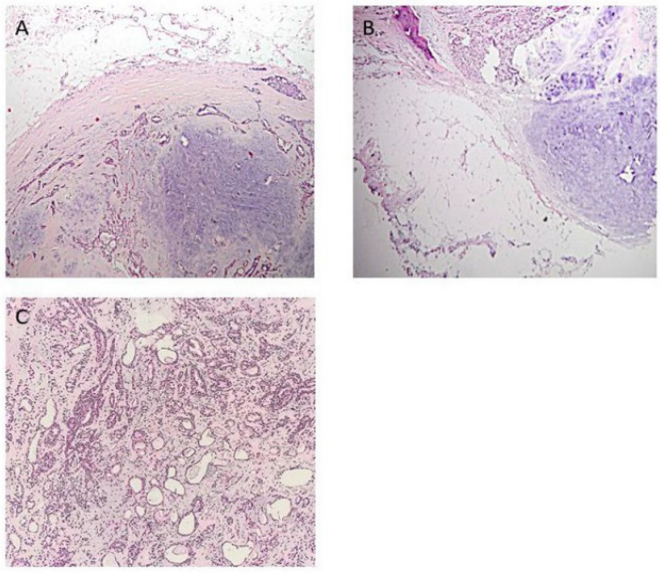


Figure 4: A. The cartilage mucous stroma was adjacent to the breast adipose tissue, and boundary was clear. × 40; **B.** Cartilage tissue presented at adenomyoepithelioma region; **C.** adenomyoepithelioma region.

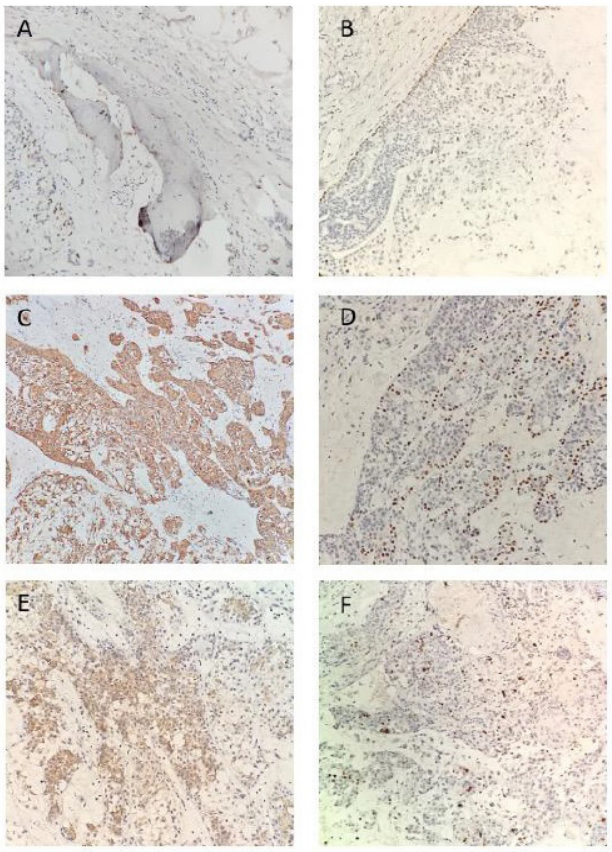


Figure 5: A. P63 presented negative for partial myoepithlium × 100. **B.** P63 was positive for myoepithlium around ducts ×200. **C.** Diffused positive for CK5/6. **D.** Mature squamous epithelial and myoepithelial cells presented positive for P63. **E.** Partial positive for CK8/18. F. 10% of cells showed ki67 positive. ×100.

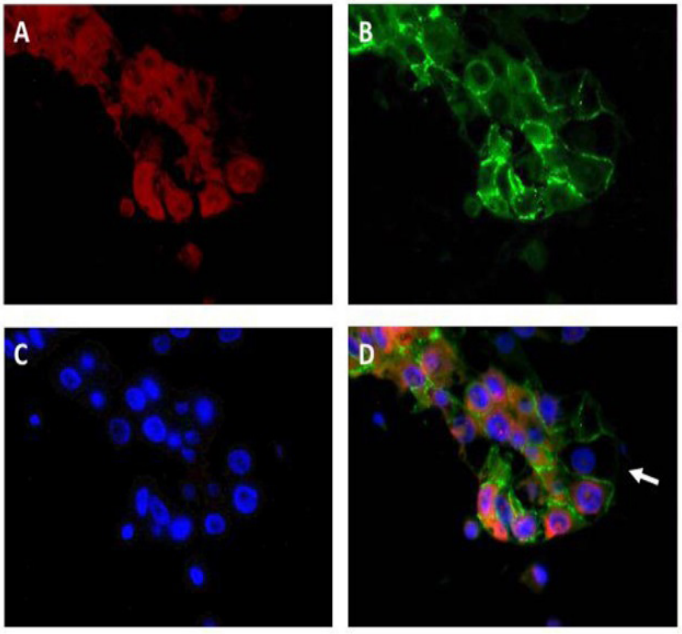


Figure 6: Immunofluorescence study showed scattered CD44+ (green) / CD24- (red) tumor cells counting about 5%. **A:** Staining for CD24; **B:** Staining for CD44; **C:** DAPI; **D:** Merge.

4. Discussion

PA is a common benign tumor of the salivary glands. A benign mixed tumor of the breast was first reported in 1906 by Lecène, [6] and in 1969 Smith and Taylor discovered 9 cases of breast tumor with components of cartilage and bone reported in the files of the Air Force Information Program (AFIP) [7]. However, they did not make a diagnosis of PA, but instead classified the tumors as intraductal papillomas with interstitial bone and cartilage metaplasia, and described the myoepithelial cells as proliferating to form special mesenchymal elements. They also suggested that multifocal tumors might originate from multiple intraductal papillomas [8,9] and that the cartilage and bone matrixes were rare characteristics of intraductal papillomas. In 1978 Sheth reported a similar case and was the first to call the tumor a PA of the breast [10]. Sheth and other researchers asserted that myoepithelial cells play a critical role in tumorigenesis because they are multipotent and can differentiate to mucusproducing cells, fibroblasts, and cartilage [11]. Breast PA is consistently associated with intraductal papilloma, and has been regarded as a type of aberrant intraductal papilloma, [2,12] although some researchers believe that PA is variant of ductal adenoma or multi-nodular myoepithelioma, [4] and others have inferred that PA is an independent pathological type in breast tumor always accompanying with intraductal papilloma or ductal carcinoma in situ (DCIS) [13]. The histological and immunohistochemical findings in our case indicated that breast PA originates from the inner lining the large ducts, and in this case, it occurred simultaneously in three ducts. In general, breast progenitor cells are CK5/6+ and CK8/18-; intermediate-type myoepithelial cells and squamous cells are CK5/6+ and p63+; and intermediate-type adenoepithelial cells are CK5/6+ and CK8/18+. Correspondingly, in our case, the tumor showed diffuse CK5/6 positivity and local p63 and CK8/18 positivity. The finding that most CK5/6+ cells are mature and immature squamous cells, intermediate-myoepithelial cells, intermediate-adenoepithelial cells, and progenitor cells may be indicative of the process whereby the stem cells differentiate to multipotent cells and that by which immature cells differentiate to mature cells. CD44+/CD24- cells in breast cancer have been identified as cancer stem cells, which also originate from breast progenitor cells, [14,15] and we observed CD44/CD24 cells scattered in this case indicating that the presence of breast cancer stem cells in this tumor. The mixed histological character of the PA in our case, which included not only squamous epithelium, glandular epithelium, and myoepithelium, but also immature squamous epithelium, intermediate-type adenoepithelial epithelium, intermediate-type myoepithelium, bone and cartilage, and breast cance stem cells, is also consistent with a multipotent progenitor cells as the tumor origin. Moreover, our finding supports the notion that the histological pattern of breast PA actually differs from that of SGPA in that breast PAs are more often derived from large ducts, and the ductal epithelium proliferates to form a papillomatous region that is a morphologic type of PA. Furthermore, the genomic changes that have been observed in SGPA, including amplifications of HMGA2 and MDM2 gene, deletions of 5q23.2–q31.2, and amplifications of 8q12.1 (PLAG1) and 8q22.1–q24.1 (MYC), have not been observed in breast PA [16]. This suggests that breast PA is an independent tumor that shares certain histological characteristics with SGPA. In fact, Rakha et al have recently proposed that breast PAs should instead be called pleomorphic adenoma-like tumors of the breast [5].

To date, including our case, there have been only 86 cases of breast PA reported in the literature, and to the best of our knowledge, ours is the first report of a breast PA accompanied by squamous epithelial hyperplasia. Breast PA occurs mostly in women, with a female:male ratio of 10:1, but 3 cases have been reported in men [2,12,17-19]. The age of onset ranges from 19 to 85 years, [13,20] and it is most commonly reported in postmenopausal women. Breast PA tends to occur close to areola, consistent with an origin in the large ducts, and it usually presents as an isolated lump [21-23] ranging in size ranges from 0.6 cm to 17 cm and most often larger than 2 cm [18,24,25]. The reason that fewer cases of breast PA have been reported in Asia than in Europe may be linked to differences between Asian and Western diets [8]. There were 8 cases of breast PA reported in China from 1999 to 2009, and one of them was diagnosed as malignant. The age of onset ranged from 19 to 71 years, and all of the patients were women, 4 premenopausal and 4 postmenopausal. Grossly, two of the tumors were mixed cystic and solid type, five had fibrous sheaths, and one infiltrated the breast tissue. All of the tumors were reported as suspected breast cancers on ultrasound, which highlights the difficulty in differentiating breast PA from breast cancer by ultrasound and MRI.

4.1. The Differential Diagnosis of Breast PA Includes

1. Metaplastic carcinoma. Breast PA is easily misdiagnosed as metaplastic carcinoma, particularly if the central part of tumor is sampled by puncture core biopsy. In contrast, frozen-section pathology after excision biopsy can yield more information, but sometimes frozen mucinous stroma, bone components, and epithelial atypia will make the pathological diagnosis more difficult. Metaplastic carcinoma containing heterologous cartilage and bone elements is usually a high-grade malignancy that shows an invasive growth pattern and high-grade cellular atypia. Compared to PA, there will be more mitoses, especially pathological mitoses, and necrosis, can also be observed. There are no benign adenomyoepithelioma and papilloma components, and the boundary will not be clear. Furthermore, breast PA originates from large ducts, and general metaplastic carcinoma does not. Besides regions of squamous metaplasia, cartilage and bone, papilloma, and benign areas of adenomyoepithelioma, the presence of ADH and DCIS in surround-

ing breast tissue can be used to identify metaplastic carcinoma.

2. Carcinoma ex-pleomorphic adenoma of the breast. At present, there are no clear diagnostic criteria for carcinoma ex-pleomorphic adenoma of the breast. If high grade atypia of epithelial cells, more mitoses, pathologic mitoses, necrosis, and invasive growth (capsule and vessel invasion) are present in a salivary gland, the diagnosis is possible. Moreover, components of mesenchymal cartilage and bone are not the evidence of canceration.

3. Adenomyoepithelioma. Adenomyoepithelioma is characterized by the proliferation of myoepithelial cells around the lumen. Structurally, it presents lobular, papillary, tubular, and mixed growth types. The tubular component is major. When lobular and spindle cell type adenomyoepithelioma accompanies myxomatous degeneration, it should be identified with breast PA. Myxochondroid stroma, hyaline cartilage, and ossification are usually observed in the stroma of PA, but rarely observed in adenomyoepithelioma. Besides metaplasia of squamous epithelium and sebaceous differentiation, apocrine metaplasia is also present.

4. Papilloma associated with cartilage metaplasia. Papilloma is characterized by a dense and branched papillary structure with a vascularized fibrous central axis, monolayer myoepithelial cells, and covered glandular epithelial cells. It is sometimes associated with usual ductal hyperplasia. Apocrine metaplasia and squamous metaplasia are always observed, the latter is most common in infarcted areas. Rarely, myxomatous degeneration and cartilage metaplasia are observed, but with no ossification or adenomyoepithelioma. Thus, the morphology of this tumor type is less diverse than that of PA, which presents various epithelial and mesenchymal components, with regions of ossification and adenomyoepithelioma commonly.

Generally, breast PA has a favorable prognosis. Sato et al reported local recurrence in 2 cases. [23] Willen, Moran, and Sheth all reported multifocal cases [8, 13, 10]. Hayes et al described 3 cases of carcinoma ex-pleomorphic adenoma of the breast without lymph node metastases of lymph node. In that small series, 1 patient received chemotherapy (adriamycin + cyclophosphamide) and remained recurrence- and metastasis-free during 4.5 years of follow-up; 1 patient received radiotherapy with a 6-month follow-up; and 1 did not receive any adjuvant treatment and had no recurrence or metastasis during a short (4-month) follow-up. To date, the metastatic of carcinoma expleomorphic adenoma of the breast has not been reported [26-33]. These outcomes suggests that even malignant ex-pleomorphic adenoma can have a good outcome. As such, excision of breast PA with an adequate surgical margin is the best curative option [34]. However, although breast PA has a more favorable prognosis, the nature andbiological behavior of the tumor may be another matter. Yamaguchi points out that the absence of peripheral myoepithelial cells in breast PA and the pattern of local p63 positivity suggests these cells are differentiating to basal/myoepithelial cells, but not to peripheral myoepithelial cells that can protect tumor cells [35]. In our case, there was myoepithelium around large ducts in the tumor, some of which proliferated to form cuboidal myoepithelium, there was p63 and CK5/6 is positivity, and CK7 was negative. These findings are helpful for determining which myoepithelium component will play an important role in protecting the tumor. P63, calponin, and S-100 negativity in cells around a tumor nodule suggests a lack of myoepithelial cells in the tumor, and the presence of myoepithelium is generally thought to intercept tumor cells; that is, it is an indicator of a better prognosis. However, some tumors can also have a good prognosis even if the myoepithelium is absent, for example, encapsulated papillary carcinoma of the breast is characterized by malignant epithelial proliferation but has favorable prognosis and can be treated with adequate local surgical therapy. In our case, we observed that multi-nodular growth, lack of myoepithelium, and highgrade cell atypia. All of these suggested that the tumor had invasive potential. Taken together with our results, we believe that breast PA accompanied by hyperplasia is a type of low-grade malignancy that may originate from progenitor cells. We also believe that PA associated with hyperplasia of squamous epithelium, marked cell atypia, high nuclear grade, or incomplete myoepithelium could increase the risk of lymph node metastasis. Future case reports may support these findings.

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