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BRIEF REPORT

Spiradenoma of the breast: a rare diagnostic pitfall in the evaluation of solid-basaloid breast lesions with a dual cell population

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Abstract

Breast spiradenoma is extremely rare, with only 4 cases reported previously. We describe an instructive case of breast spiradenoma resembling adenoid cystic carcinoma (AdCC). A 71-year-old woman underwent excisional biopsy of a breast mass after a conclusive diagnosis was unable to be obtained from core needle biopsy showing an AdCC-like pattern. Histopathologically, the lesion demonstrated solid and cribriform foci comprising basaloid cells, luminal cells, and eosinophilic hyaline material, reminiscent of solid-basaloid AdCC, alongside convoluted lumens, stromal edema, lymphocytic infiltration, and c-kit negativity. On molecular analysis, neither *MYB* fusion genes nor *CYLD* gene abnormalities were identified. These results were supportive of spiradenoma. Salivary gland– and skin adnexal–type tumors are challenging to diagnose due to morphological overlaps. This case, highlighting histopathological and molecular features, shows that breast spiradenoma can be a diagnostic pitfall among the differential diagnoses of AdCC.

Keywords Spiradenoma · Skin adnexal–type neoplasms · Adenoid cystic carcinoma · Breast tumor

Introduction

A small proportion of breast tumors are reminiscent of salivary gland– or skin adnexal–type neoplasms. This can be understood as mammary glands are regarded as modified sweat glands, with morphological similarity between sweat and salivary gland tumors. Given their rarity, skin adnexal–type tumors are not included in the World Health Organization Classification of Tumours of the Breast, 5th edition [1]. Spiradenoma of the breast, a skin adnexal–type tumor, is extremely rare and thus often overlooked as a differential diagnosis of breast tumors. Here, we report a rare case of breast spiradenoma which had to be discriminated from adenoid cystic carcinoma (AdCC), and describe histopathological and molecular features of this pathological entity.

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Case presentation

A 71-year-old woman presented with a 12-mm left breast mass detected on screening mammography. Ultrasonography revealed a partially ill-defined hypoechoic mass with an internal mixture of cystic and solid components and intramammary localization of the mass (Fig. 1a). Contrast-enhanced magnetic resonance imaging demonstrated a well-defined mass with signal hyperintensity on T2-weighted imaging and early enhancement of the peripheral area of the mass (Fig. 1b).

Core needle biopsy specimen

Microscopically, sections showed solid, trabecular, and cribriform epithelial nests, partially arranged in a mosaic pattern

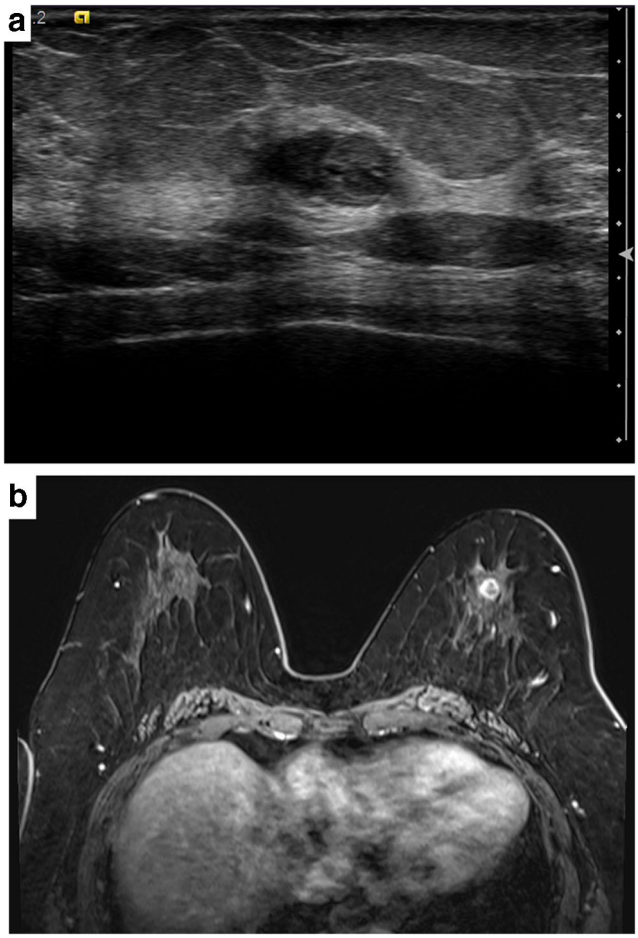

Fig. 1 Imaging findings. **a** Ultrasonography of the hypoechoic mass. As the mass locates deep to the skin and the Cooper ligament is identified between the skin and the mass, it proves intramammary localization of the lesion. **b** Contrast-enhanced magnetic resonance imaging shows a well-defined, peripherally enhancing mass

(Fig. 2a). The epithelial nests comprised two cell populations: basaloid cells with scant cytoplasm distributed at the periphery, and slightly larger cells with eosinophilic cytoplasm at the center of the nests. No nuclear atypia was evident and sparse mitotic figures were present. Some nests were surrounded by eosinophilic hyaline material, while others had pseudolumens containing eosinophilic spherules (Fig. 2b). No myxoid material was seen within the lesion.

On immunohistochemistry, dual cell populations of luminal cells and basaloid/myoepithelial cells were confirmed according to the distribution of cells positive for cytokeratin (CK)7, p63, CK14, and smooth muscle actin (Fig. 2c, d). Negative results were obtained for estrogen receptor, progesterone receptor, human epidermal growth factor receptor 2, and c-kit on tumor cells.

Fluorescence in situ hybridization (FISH) was used to investigate t(6;9)(q22-23;p23-24) translocation using ZytoLight SPEC MYB Dual Color Break Apart Probe (ZytoVision, Bremerhaven, Germany), but no MYB split signals were identified (Fig. 2e).

The dual cell population, eosinophilic hyaline material, and eosinophilic spherules were reminiscent of solid-basaloid AdCC, but the mosaic pattern, lack of myxoid material, c-kit negativity, and absence of any MYB split signals undermined this consideration. Although an extremely rare tumor in the breast, these findings suggested a possible cylindroma. As the actual diagnosis remained unclear on the limited core material, excision to allow complete histological evaluation of the lesion was recommended.

Excisional biopsy specimen

The cut surface of the specimen showed a well-circumscribed white mass measuring 11 × 10 × 10 mm with a hemorrhagic area (Fig. 2f). The mass was within the breast parenchyma.

The tumor was well-demarcated and not attached to the skin, but was located within the breast tissue (Fig. 2g). In addition to the core needle biopsy (CNB) findings, cystic changes with hemorrhage, stromal edema, and sparse lymphocytic infiltration (Fig. 2h) were identified within the tumor. The jigsaw-puzzle arrangement characteristic of cylindroma was not apparent, but eosinophilic hyaline material was seen around individual nests. Slit-like and convoluted true lumens were occasionally identified (Fig. 2h). Findings of cystic changes and intratumoral lymphocytic infiltration were more suggestive of spiradenoma than cylindroma.

Profiling of 160 cancer-related genes (including the *CYLD* gene) by the next-generation sequencing (NGS) using formalin-fixed paraffin-embedded tumor sections and peripheral blood was performed as previously reported [2]. These investigations revealed absence of any mutations or loss of heterozygosity in the *CYLD* gene.

Ten months after excisional biopsy, local recurrence was not identified.

Discussion

In the present case, we report potential pitfalls to the differential diagnosis of AdCC of the breast. AdCC is rare, comprising < 0.1% of breast carcinomas [3]. AdCC histologically resembles the salivary gland counterpart and is generally a triple-negative-type tumor with indolent behavior. Differential diagnoses for AdCC usually include invasive cribriform carcinoma and collagenous spherulosis. However, this case highlighted the fact that skin adnexal–type neoplasms such as spiradenoma should be included among the differential diagnoses of AdCC, despite their rarity. Spiradenoma of the breast, other than that originating from the skin overlying the breast, is extremely rare. Only 4 cases have been reported previously

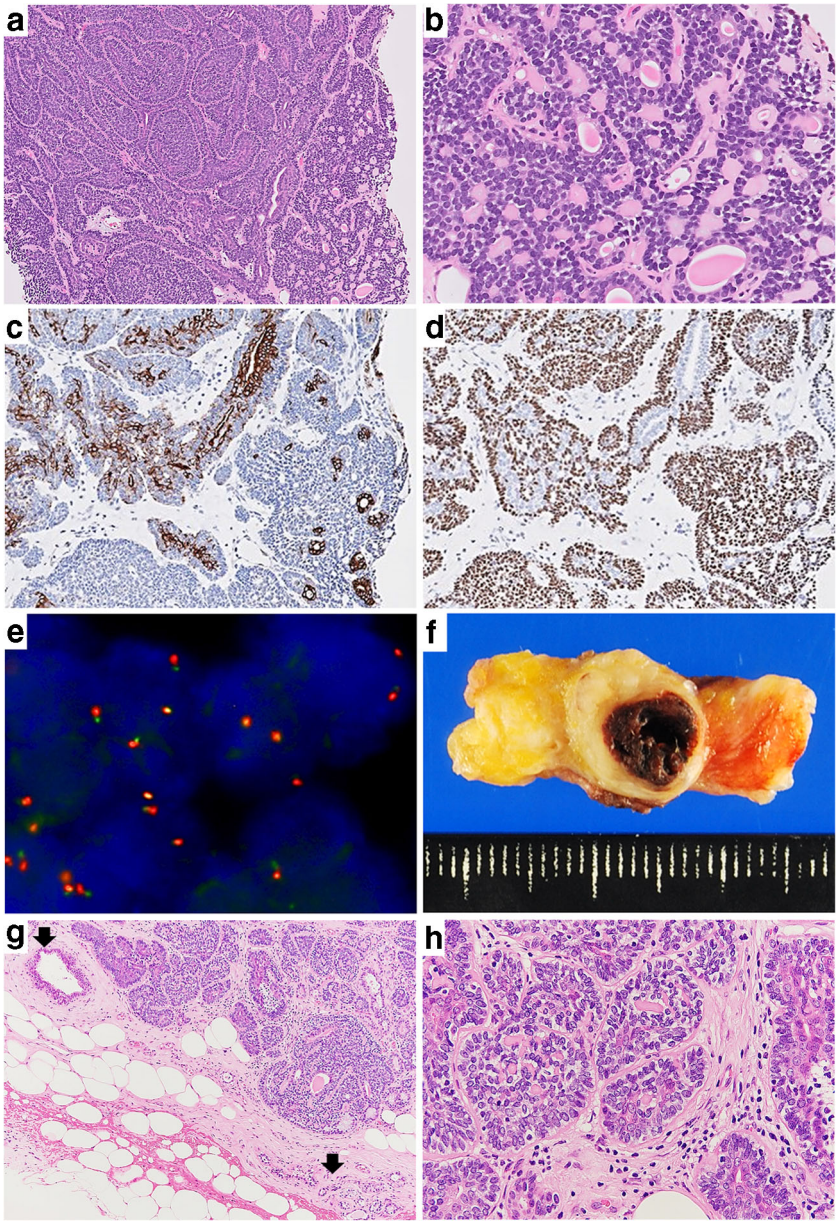

Fig. 2 Histopathology of the CNB specimen (**a**-**e**) and excisional biopsy specimen (**f**-**h**) . **a** The section shows trabecular, solid, and cribriform nests. Solid nests are arranged in a mosaic pattern. **b** Cribriform nests mainly comprise basaloid cells and have pseudolumens with eosinophilic spherules. **c** CK7 stain highlights luminal structures. **d** Basaloid cells/myoepithelial cells are positive for p63. **e** The tumor is negative for *MYB* rearrangement by FISH. Green and orange signals label points proximal and distal to the MYB break point region, respectively. **f** A macroscopic view of the lesion displays a well-circumscribed white mass with hemorrhagic areas. **g** The section shows normal breast tissue (arrow) in the border of the tumor. **h** The tumor demonstrates cribriform nests with eosinophilic hyaline materials, irregular nests comprising two cell populations (basaloid cells and luminal cells) with slit and convoluted lumens, and stroma with lymphocytic infiltration

in the English literature [4–7]. Those reports discussed malignant transformation from spiradenoma [4, 5], its biological behavior [6], and cytological findings [7], whereas our case highlighted the diagnostic clue of spiradenoma. The differential diagnosis of spiradenoma includes breast tumors with dual cell populations, such as cylindroma, adenomyoepithelioma, and AdCC. In particular, spiradenoma can resemble AdCC, due to common histological findings of architectural patterns, dual cell populations, and eosinophilic basement membrane material. Spiradenoma could thus be misdiagnosed as AdCC, especially from limited biopsy specimens. In this case, an important point was that the common findings mentioned above were seen in part of the lesion, while findings such as slit-like and convoluted true lumens mimicking coiled ducts, stromal edema, and lymphocytic infiltration in other areas were characteristic of spiradenoma rather than AdCC. One additional point is that both tumors usually appear circumscribed mass radiologically and macroscopically, but at low power magnification, spiradenoma shows one or several circumscribed nodules; in contrast, AdCC demonstrates a diffusely infiltrating growth pattern. These findings might thus represent helpful clues for the diagnosis (Table 1).

The *MYB-NFIB* fusion gene has been revealed in 12.5–100% of breast AdCC [8, 9], 0–67% of dermal cylindromas [10, 11], and 0% of dermal spiradenomas [11]. The *MYB* FISH result in our case was in keeping with previous results reported for the *MYB-NFIB* fusion gene in dermal spiradenoma. Although *MYB* FISH may be helpful in the

Table 1 Comparison of pathological features of breast tumors with dual cell population

	Spiradenoma	Cylindroma	Adenomyoepithelioma	Adenoid cystic carcinoma
Tumor border	Well defined	Well defined	Well defined	Well defined, irregular
Architecture	Trabecular, reticular, solid, tabular with slit-like and convoluted true lumens, cystic, cribriform	Jigsaw-puzzle arrangement	Lobulated nodule, papillary, tubular, solid	Cribriform tubular, solid, trabecular, reticular
Cell composition	Pale cytoplastic Basaloid	Pale cytoplasmic Basaloid	Luminal epithelial Myoepithelial (clear, spindle, myoid)	Luminal epithelial Myoepithelial/basaloid
Stroma	Eosinophilic basement membrane material, edema, lymphocyte	Eosinophilic basement membrane material, edema	Dense collagenous myxochondroid	Myxoid, eosinophilic basement membrane material
Immunohistochemistry	Pale cytoplasmic - CK7, CK19(+) Basaloid - p63(+)	Pale cytoplasmic epithelial - CK7, CK19(+) Basaloid - p63(+)	Luminal epithelial - CK7, EMA(+) Myoepithelial basaloid - p63, CK14, SMA, Calponin, S100	Luminal epithelial - CK7, CD117(+) Myoepithelial, basaloid - p63. CK14, SMA, CD117(+) ER/PR/HER2 negative
Diagnostic molecular pathology	Germline or somatic *CYLD* mutations (no reports were available on breast spiradenoma)	Germline or somatic *CYLD* mutations *MYB-NFIB* fusion gene (no reports were available on breast spiradenoma)	Few studies were available	*MYB-NFIB* fusion gene (12.5–100%)

differential diagnosis of AdCC, emphasis is needed regarding the fact that *MYB-NFIB* fusion genes are not detected in all AdCC cases, and some breast cylindromas may demonstrate the *MYB-NFIB* fusion gene. Thus, AdCC and cylindroma cannot be ruled out purely according to *MYB* FISH results. However, the fact that common fusion gene has been identified between AdCC and cylindroma is interesting and potentially important in explaining the genetic link between these two tumors and their pathogeneses.

The patient in this case had no clinical history or symptoms indicative of Brooke-Spiegler syndrome, an autosomal-dominant inherited disorder characterized by multiple lesions in a mixture of cylindroma, spiradenoma, and trichoepithelioma with germline *CYLD* mutations. As *CYLD* somatic mutations and/or somatic loss of heterozygosity has also been identified in sporadic dermal cylindromas and spiradenoma [11, 12] and AdCC lacks *CYLD* somatic mutations [13], the presence of *CYLD* gene abnormality can help differentiate between AdCC and cylindroma/spiradenoma [14]. Rashid et al. revealed somatic or germline alterations of the *CYLD* gene in 14 of the 14 dermal cylindromas and 4 of the 16 dermal spiradenomas [11]. The absence of *CYLD* gene alterations thus could not be used to exclude spiradenoma.

In this report, we describe a case of breast spiradenoma with a diagnostic approach integrating histopathology, immunohistochemistry, FISH, and NGS. As AdCC is typically treated by complete excision with sentinel lymph node sampling, pathologists should keep spiradenoma in mind as a possible differential diagnosis of AdCC to avoid overtreatment.

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Author contributions NA provided clinical information and specimens. HM and NA wrote the manuscript. RT performed and analyzed *MYB* FISH and NGS. TPH provided opinions for diagnosis and manuscript review. All authors made substantial contributions to the conception, design, and drafting of the work.

Compliance with ethical standards

This study was part of a research project approved by the ethics committees at Nakagami Hospital (2016028-1).

Conflict of interest The authors declare that they have no conflict of interest.

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