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Brief Communication

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Malignant Apocrine Lesions of the Breast: Multimodality Imaging Findings and Biologic Features

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ABSTRACT

The apocrine morphology of the breast is observed in a broad pathological spectrum, ranging from benign cysts to invasive carcinomas. However, the number of clinical research investigating malignant apocrine lesions is limited. This study retrospectively reviewed the data of patients with malignant apocrine lesions admitted in a tertiary center between January 2004 and December 2021, based on the radiology-pathology correlation and the recent advances in their status to enhance the therapeutic implications of androgen receptor (AR). Among the 37 patients with lesions, 27 (73.0%) had triple-negative subtypes with predominant AR expression. The radiological features of malignant apocrine lesions did not differ from those of typical invasive ductal carcinoma or ductal carcinoma in situ. This study demonstrated that knowledge on the imaging features of malignant apocrine lesions and their histological basis could enhance the adoption of new targeted therapies in patients with this particular type of breast cancer.

Keywords: Apocrine Glands; Breast; Carcinoma; Receptors, Androgen

INTRODUCTION

Apocrine morphology is a common pathological finding characterized by enlarged cuboidal or columnar cells with abundant eosinophilic cytoplasm, apical blebs or snouts, and round nuclei, and is identified in benign, atypical, and malignant lesions of the breast [1]. Although benign apocrine lesions are frequently encountered in daily practice, an atypical and malignant spectrum of this disease is rare.

Currently, numerous studies have been conducted to identify novel therapeutic strategies for patients with breast cancer who do not respond to standard therapy but have a potential targetable pathway such as the androgen receptor (AR) signaling pathway. The apocrine epithelium of the breast shows consistent expression of AR, and demonstrates

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Conflict of Interest
The authors declare that they have no competing interests.

Author Contributions
Conceptualization: Lee HJ, Lim HS; Data curation: Lee HJ, Kang SW; Formal analysis: Jeong WG, Lee JE; Resources: Lee JS, Park MH; Supervision: Lim HS; Writing - original draft: Lee HJ; Writing - review & editing: Lee HJ, Kang SW, Lee JS, Park MH, Lim HS.

estrogen receptor (ER)-negative and progesterone receptor (PR)-negative profiles. Therefore, AR has been used as a diagnostic hallmark of apocrine carcinoma [2]. However, owing to the insufficient knowledge on the correlation between apocrine morphology, immunohistochemical (IHC) staining characteristics, genetic profiles, and data regarding the clinical manifestations, especially the radiologic findings of malignant apocrine lesions, which are less well defined, little is known about the exact profiling of apocrine carcinoma. Therefore, this study aimed to elucidate the clinical imaging findings and pathological features along with the IHC staining characteristics of malignant apocrine lesions based on the data obtained from an 18-year review of the biopsy and surgical specimens of malignant apocrine lesions and to summarize the previous literature on this field.

METHODS

We retrospectively reviewed the data of patients with malignant apocrine lesions who were admitted in our hospital between January 2004 and December 2021. Appropriate Institutional Review Board (IRB) approval was obtained from Chonnam National University Hwasun Hospital (IRB No. CNUHH-2021-057), and the requirement for obtaining informed patient consent was waived.

The pathological specimens were assessed by a single breast pathologist (with 27 years of experience) through cytomorphological examination and IHC staining. An automated IHC staining system was used (Bond-Max system; Leica Microsystems, Bannockburn, IL, USA) with the following primary monoclonal antibodies: ER (1:50, 1D5; Dako, Glostrup, Denmark), PR (1:50, PgR636; Dako), human epidermal growth factor receptor 2 (HER2) (1:200, CB11; Leica Microsystems), Ki-67 (1:100, MIB-1; Dako), AR (1:100, AR441; Dako), and gross cystic disease fluid protein 15 (GCDFP-15) (clone 23A3, dilution 1:100; Leica Biosystems, Buffalo Grove, IL, USA). GCDFP-15, a prolactin-induced protein, is a product of the AR target gene prolactin and is frequently used as a marker of apocrine differentiation [3].

In order to establish a definite diagnosis of apocrine ductal carcinoma *in situ* (ADCIS), an atypical apocrine proliferation of > 2 mm and a fully developed architectural pattern (solid, cribriform, or micropapillary) indicative of DCIS were used as criteria [4]. Furthermore, carcinoma with apocrine differentiation was defined as an invasive carcinoma characterized by presence of apocrine tumor cells detected under a light microscope.

Two breast radiologists (with 4 and 18 years of breast imaging experience, respectively), who were blinded to the clinicopathologic information, reviewed the results of multimodality imaging examinations, including mammography (mass only, mass with microcalcification, calcification only, focal asymmetry, and normal), ultrasound (mass [shape, margin, and echogenicity], non-mass, and no delineation), and magnetic resonance imaging (MRI) (mass [shape, margin, internal enhancement], non-mass enhancement). A non-mass lesion detected on ultrasound denoted a focal area of heterogeneity that does not have a conspicuous margin or shape and cannot be classified as a "mass" based on the Breast Imaging Data and Reporting System (BI-RADS) developed by the American College of Radiology [5].

RESULTS

Among the 10,482 patients who underwent surgical treatment for primary breast carcinoma between 2004 and 2021, we retrospectively collected the data of 20 and 17 patients diagnosed with carcinoma with apocrine differentiation (up to 0.2% among invasive carcinoma) and ADCIS (up to 0.9% among DCIS), respectively. Among the 20 patients who had carcinoma with apocrine differentiation, one was diagnosed with ADCIS by core-needle biopsy, and the diagnosis was upgraded to invasive carcinoma after surgery. The prevalence of malignant apocrine lesions was within the previously reported prevalence rate of apocrine carcinoma (0.3%–4%) [6,7].

The clinicopathological and multimodal imaging features of the patients are presented in **Table 1**. The patients' mean age was 58.5 years (range: 35–89 years). Additionally, two patients showed axillary nodal metastases, while one with recurrent case presented with delayed axillary nodal metastasis.

Among the patients diagnosed with carcinoma with apocrine differentiation, 17 had triple-negative breast cancer (TNBC) (85%), 2 had HER2-positive cancer (10%), and 1 had luminal cancer (5%) based on the results of IHC staining. Among the patients with ADCIS, 10 had a triple-negative subtype (58.8%), 4 had an HER2-positive subtype (23.5%), and 3 had a luminal subtype (17.6%). Although most carcinomas with apocrine differentiation are grade 1 or 2 tumors, most patients with ADCIS had grade 3 tumors.

Nineteen patients with carcinoma with apocrine differentiation showed AR positivity (95%); among the patients with TNBC (n = 17), 16 showed AR positivity (94.1%). All ADCIS patients showed AR positivity (100%). Twelve patients with carcinoma with apocrine differentiation showed GCDFP-15 positivity (60%), while seven ADCIS patients showed GCDFP-15 positivity (41.2%).

The imaging features of carcinoma with apocrine differentiation were as follows: mass only (n = 9, 45%), mass with microcalcifications (n = 3, 15%), microcalcifications only (n = 1, 5%), focal asymmetry (n = 3, 15%), and normal (n = 2, 10%) on mammography (two patients had no mammogram data); mass (n = 17, 85%), non-mass (n = 1, 5%), and no delineation (n = 1, 5%) on ultrasound (one patient had no ultrasound data); and mass (n = 11, 55%) and non-mass enhancement (n = 3, 15%) on MRI (six patients had no MRI data; **Table 1**). The mean size of the enhancing lesion on MRI was 2.1 cm (range, 0.6–4 cm). Thirteen patients with carcinomas with apocrine differentiation showed an oval shape lesion, 10 showed a relatively circumscribed margin, and three showed a complex cystic and solid pattern on ultrasound; seven showed an oval shape lesion, four showed a relatively circumscribed margin, and six showed rim enhancement on MRI.

The imaging features of ADCIS were as follows: mass only (n = 2, 11.8%), mass with microcalcifications (n = 2, 11.8%), microcalcifications only (n = 2, 11.8%), focal asymmetry (n = 3, 17.6%), and normal (n = 6, 35.3%) on mammography (2 patients had no mammogram data); mass (n = 5, 29.4%), non-mass (n = 10, 58.8%), and no delineation (n = 1, 5.9%) on ultrasound (1 patient had no ultrasound data); and mass (n = 3, 17.6%) and non-mass enhancement (n = 10, 58.8%) on MRI (4 patients had no MRI data; **Table 1**). The mean lesion size on MRI was 2.2 cm (range, 0.6–7.5 cm). The images of ADCIS showed fewer mass-forming characteristics than those of carcinoma with apocrine differentiation. The representative images of carcinoma with apocrine differentiation and ADCIS are shown in **Figures 1** and **2**, respectively.

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Table 1. Clinicopathologic and multimodality imaging features of malignant apocrine lesions

Characteristics	Carcinoma with apocrine differentiation (n = 20)	ADCIS (n = 17)
Age (yr)	61.1 ± 11.1	58.6 ± 13.0
Symptom		
Palpability	10 (50.0)	6 (35.3)
No symptom	10 (50.0)	11 (64.7)
Immunohistochemistry subtype		
Luminal	1 (5.0)	3 (17.6)
HER2-positive	2 (10.0)	4 (23.5)
Triple-negative	17 (85.0)	10 (58.8)
AR positivity		
Yes	19 (95.0)	17 (100.0)
No	1 (5.0)	0 (0.0)
GCDFP-15 positivity		
Yes	12 (60.0)	7 (41.2)
No	8 (40.0)	10 (58.8)
Histologic grade		
Grade 1	5 (25.0)	1 (5.9)
Grade 2	12 (60.0)	3 (17.6)
Grade 3	3 (15.0)	13 (76.5)
Ki-67 (%)	5 (1–40)	5 (3–20)
Axillary nodal metastasis		
Yes	2 (10.0)	0 (0)
No	18 (90.0)	17 (100.0)
Size of invasive component (mm)	13.8 ± 10.2	N/A
Associated DCIS		
Yes	14 (70.0)	N/A
No	6 (30.0)	
Extensive intraductal component*		
Present	3 (27.3)	N/A
Absent	8 (72.7)	
Mammogram finding†		
Mass only	9 (45.0)	2 (11.8)
Mass with microcalcifications	3 (15.0)	2 (11.8)
Microcalcifications only	1 (5.0)	2 (11.8)
Focal asymmetry	3 (15.0)	3 (17.6)
Occult	2 (10.0)	6 (35.3)
Ultrasound finding‡		
Mass	17 (85.0)	10 (58.8)
Non-mass	1 (5.0)	5 (29.4)
No delineation	1 (5.0)	1 (5.9)
Magnetic resonance imaging finding§		
Mass	11 (55.0)	3 (17.6)
Non-mass enhancement	3 (15.0)	10 (58.8)

Values are presented as mean ± standard deviation, number (%), or median (range).
ADCIS = apocrine ductal carcinoma *in situ*; HER2 = human epidermal growth factor receptor 2; AR = androgen receptor; GCDFP-15 = gross cystic disease fluid protein 15; DCIS = ductal carcinoma *in situ*; N/A = not applicable.
*The pathologic data of extensive intraductal component was not available for three patients with associated DCIS.
†Each 18 and 15 mammograms were available for patients in the carcinoma with apocrine differentiation and ADCIS groups.
‡Each 19 and 16 ultrasound images were available for patients in the carcinoma with apocrine differentiation and ADCIS groups.
§Each 14 and 13 magnetic resonance imaging were available for patients in the carcinoma with apocrine differentiation and ADCIS groups.

Table 2 shows a summary of the published articles reporting the imaging findings of patients with malignant apocrine lesions, and these findings are in line with our results [8-16]; therefore, the radiologic features of carcinoma with apocrine differentiation or ADCIS did not differ from those of typical invasive carcinoma of non-special-type or DCIS. However, invasive carcinoma presented more obvious mass formation on imaging compared with in situ lesions.

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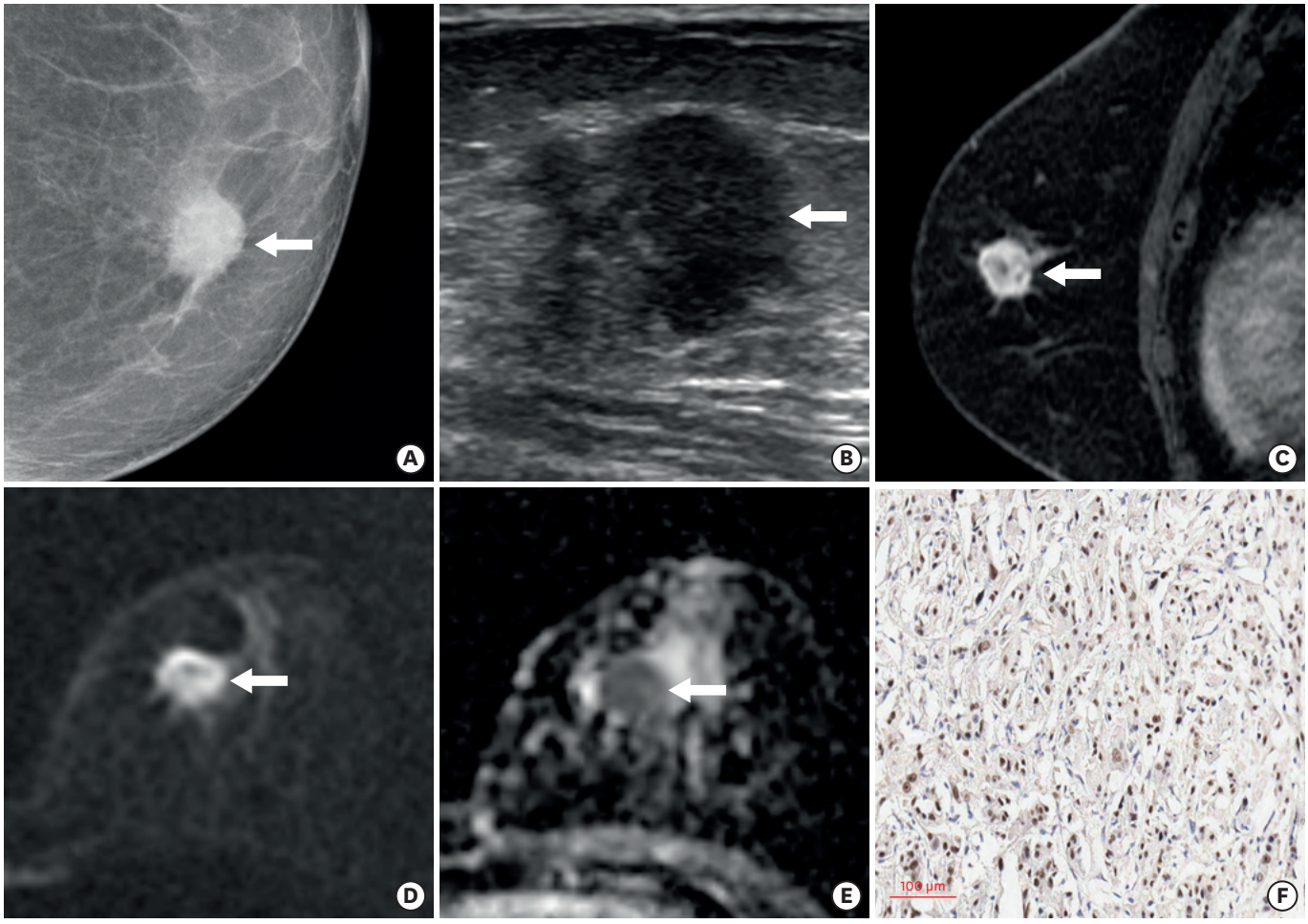

Figure 1. Carcinoma with apocrine differentiation in the left breast. (A) A craniocaudal view of the mammogram shows a 1.8-cm oval high-density mass (arrow) in the left inner breast. (B) An ultrasound image shows an oval microlobulated hypoechoic mass (arrow). (C) Sagittal contrast-enhanced magnetic resonance image shows an oval heterogeneously enhancing mass (arrow) in the left inner breast. (D and E) The diffusion-weighted image and ADC map show diffusion restriction in the mass (arrow in D and E), and the ADC value was 0.953×10^{-3} mm^2/sec. (F) The tumor cells were immunoreactive to the androgen receptor (×200).
ADC = apparent diffusion coefficient.

DISCUSSION

According to the 2019 edition of the World Health Organization (WHO) Classification of Breast Tumors, carcinoma with apocrine differentiation is defined as an invasive carcinoma characterized by apocrine tumor cells detected on light microscopy [17]. Notably, the terms "pure apocrine carcinoma," defined as malignant cells with apocrine morphology in > 90% of the cells and characterized by a distinct steroid receptor profile (ER-negative, PR-negative, and AR-positive), and "apocrine-like invasive carcinoma," which shows varying degrees of apocrine differentiation (10%–90%), have also been suggested [18]. Carcinomas with apocrine differentiation exhibit a growth pattern that is similar to that of an invasive ductal carcinoma of no special type, with a predominant solid pattern, and typically show moderate to marked nuclear pleomorphism and mitotic activity; therefore, most carcinomas with apocrine differentiation are usually grade 2 or 3 [18].

ADCIS is considered a variant of DCIS in which the cells show an apocrine morphology, but there is no unified criterion for determining the extent or grading of ADCIS [4]. It is

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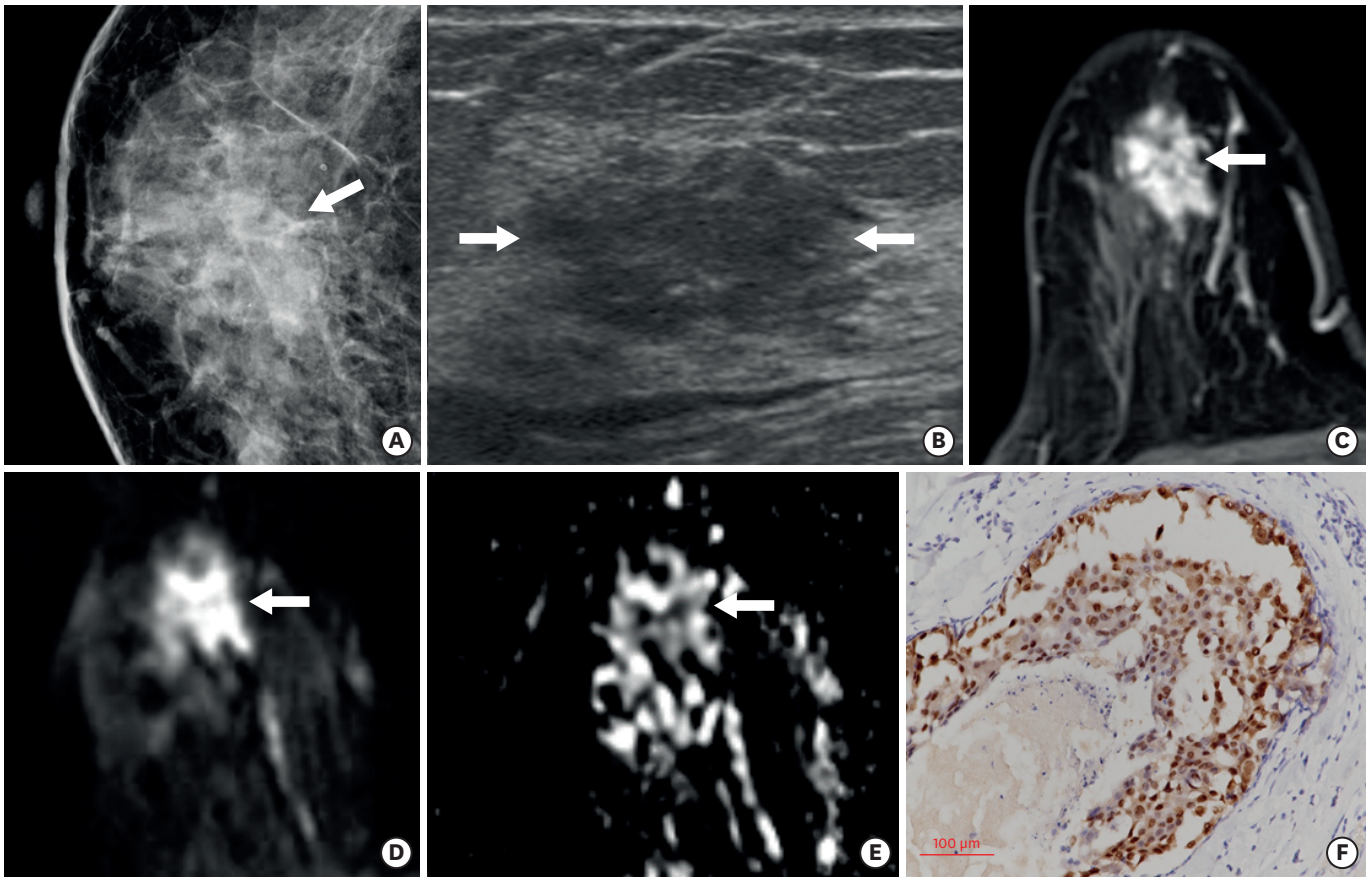

Figure 2. Apocrine ductal carcinoma in situ in the right breast. (A) A craniocaudal view of the mammogram shows focal asymmetry with regional fine pleomorphic microcalcifications in the right breast (arrow). (B) An ultrasound image shows a 1.6-cm non-mass with microcalcifications in the right breast (arrows). (C) Axial contrast-enhanced magnetic resonance image shows segmental clumped and some clustered ring non-mass enhancement in the right breast (arrow). (D and E) The diffusion-weighted image and ADC map show no significant diffusion restriction in the lesion (arrow in D and E). (F) The cells were immunoreactive to the androgen receptor and showed proliferation with micropapillary architecture, luminal necrotic debris, and periductal inflammation (×200).
ADC = apparent diffusion coefficient.

occasionally difficult to distinguish atypical apocrine lesions from ADCIS, because these lesions can also be associated with high cellularity and significant nuclear atypia. Necrosis, calcification, and periductal changes were more evident in patients with high-grade ADCIS than in other patients. ADCIS is often accompanied by invasive carcinomas with intermediate- or high-grade nuclear signatures.

This study showed that most carcinomas with apocrine differentiation and ADCIS were ER/PR-negative and AR-positive; among the patients with carcinoma with apocrine differentiation, 85% (17 of 20 cases) had TNBC. Additionally, the results commonly revealed typical TNBC imaging findings such as an oval or round shape lesion, well-circumscribed margins on ultrasound, frequent expression of complex cystic and solid patterns, and rim enhancement on MRI [19,20]. AR-positive TNBC was more likely to be associated with mammographic calcification and masses with irregular shapes or spiculated margins on ultrasound or MRI compared with AR-negative TNBC [21,22]. However, we did not statistically compare the differences in the imaging findings of malignant apocrine lesions according to AR expression owing to the limited number of patients in our cohort. Therefore, future studies with larger cohorts are warranted to further explore the differences between tumors based on AR expression.

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Table 2. Summary of published articles reporting the imaging findings of malignant apocrine lesions

Study	Age (yr)	Pathologic type	Clinical presentation	Size (cm)	Mammogram	Ultrasound	MRI
Seo et al. [8]	73	ADCIS	Palpable	8	Mass	Cyst with internal debris	Rim-enhancing cyst
Seo et al. [9]	60	ADCIS	No symptom	0.7	Normal	Irregular indistinct hypoechoic mass	N/A
Onoue et al. [10]	60	Carcinoma with apocrine differentiation	Palpable	4, 2.5	Masses	Complex cystic and solid masses	N/A
Gokalp et al. [11]	66	Carcinoma with apocrine differentiation	Palpable	3.5, 2.5	Masses with microcalcifications	Complex cystic and solid mass/irregular spiculated hypoechoic mass	N/A
Unal et al. [12]	78	Carcinoma with apocrine differentiation	Nipple retraction	1	Mass with microcalcifications	Irregular indistinct hypoechoic mass	N/A
Kim et al. [13]	61	Carcinoma with apocrine differentiation	No symptom	1	Mass	Complex cystic and solid mass	Oval, not circumscribed, heterogeneously enhancing mass
Hong et al. [14]	N/A	Carcinoma with apocrine differentiation	3†	N/A	N/A	Irregular indistinct hypoechoic mass	N/A
		ADCIS	4†	N/A	N/A	Irregular indistinct hypoechoic mass/non-mass	N/A
Seo et al. [15]	62 (48–73)*	Carcinoma with apocrine differentiation	5†	1.8 (1.2–2.2)‡	Mass/Focal asymmetry	Irregular indistinct hypoechoic mass	Irregular heterogeneously enhancing mass
Gilles et al. [16]	57 (33–88)*	Carcinoma with apocrine differentiation	17†	1.5 (1.2–5.5)‡	Mass with microcalcification/Mass only/Microcalcification only	N/A	N/A

ADCIS = apocrine ductal carcinoma *in situ*; MRI = magnetic resonance imaging; N/A = not applicable.
*Age (mean, range); †Number of cases; ‡Size (cm, range).

Carcinomas with apocrine differentiation showed more mass-forming characteristics on imaging compared with ADCIS. This finding is consistent with those of previous studies, which reported that mass formation could be one of the factors associated with the upstaging of DCIS to invasive carcinoma [23].

Although the recent WHO Classification recommends the diagnosis of apocrine carcinomas based on their morphology, Vranic et al. [24] suggested that apocrine carcinomas can be classified into two molecular subtypes according to their HER2 expression status assessed through IHC staining: HER2-positive and triple-negative subsets. The triple-negative subset showed significant overlap with the luminal androgen receptor (LAR) subtype of TNBC, which accounts for 10% of TNBC cases and is the most distinct subtype characterized by enhanced estrogen/androgen metabolism and regulation pathways and chemoresistance [25]. Additionally, the HER2-positive subset showed substantial transcriptional overlap with the "molecular apocrine tumors," which were characterized by the upregulation of AR and HER2/neu signaling without ER activation. Tumors with high AR expression levels have been continuously focused as new targetable pathways in patients who are indicated for AR-blockade therapy [26]; therefore, several clinical trials evaluating AR-targeted drugs aimed at treating non-respondent breast cancers, but with AR involvement [27,28]. However, the number of studies clarifying the relationship between apocrine morphology and AR expression or the clinical significance of malignant apocrine lesions are limited; therefore, more studies are required to understand these tumor entities in order to enhance the therapeutic implications of AR.

Our study had a typical shortcoming associated with its retrospective nature, with a relatively small number of patients due to the rarity of the disease. Therefore, the present study should be considered as a preliminary result, and further investigation in a larger population is warranted.

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In conclusion, although no pathognomonic imaging features specific to malignant apocrine lesions were revealed, this study comprehensively evaluated the histologic and imaging features of malignant apocrine lesions of the breast, to broaden the understanding of this disease entity and its potential as a future therapeutic target and to eventually achieve the ultimate goal of personalized medicine.

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