Original Investigation

Adenoid Cystic Carcinoma of the Breast: Multimodality Imaging Findings and Review of the Literature

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Rationale and Objectives: Adenoid cystic carcinoma (ACC) of the breast is a rare type of breast cancer with favorable prognosis. There is limited data on the radiological findings of this rare tumor in literature. The aim of this study is to determine the most common imaging features and review the literature.

Materials and Methods: Pathological databases of seven institutions from 2009 to 2021 were retrospectively reviewed, and patients with a diagnosis of ACC of the breast were determined. Thirteen patients whose imaging studies could be recalled from the picture archiving systems (PACS) were included in the study. Clinical and pathological findings as well as follow-up data were recorded. Radiological findings were analyzed and categorized based on BI-RADS 5th edition.

Results: There were 16 mass lesions in 13 patients (two multifocal cases, one case with recurrence). Mammography demonstrated 14 masses, while ultrasound (US) demonstrated all. MRI was available in only seven cases, with eight masses. The most common findings were round or oval shape on all modalities (78.57%–93.75%). Other frequent findings were parallel orientation (81.25%), isoechoic or hyperechoic echogenicity (62.5%), high T2 signal (87.5%), restricted diffusion (71.43%), and homogeneous enhancement (62.5%). Mammography, US and MRI showed circumscribed margins resembling a benign lesion in 35.71%, 37.5% and 50% of the lesions respectively. Three patients had a cyst-like echogenicty on US. Half of the lesions were avascular on Doppler US (6/12) and half were soft (2/4) on strain elastography. Although there were benign features on all imaging modalities seperately, all lesions could be categorized as BI-RADS 4 or 5 when the findings were combined. However 9/16 masses were BI-RADS 4A, emphasizing the subtlety of the malignant features.

Conclusion: ACC of the breast can present with findings resembling a benign lesion on different imaging modalities. Although combination of all imaging findings correctly indicated the suspicious nature of the lesions in all cases, final classification was BI-RADS 4A in most of them. Radiologists should be aware of the more frequent findings of ACC of the breast for early diagnosis. US findings of isoechoic or hyperechoic appearance, and cyst-like echogenicity have not been reported previously in literature.

Key Words: Adenoid cystic carcinoma; breast; ultrasound; mammography; MRI.

INTRODUCTION

Adenoid cystic carcinoma (ACC) is a rare type of breast cancer accounting for less than 0.1 % of malignant breast tumors (1,2). This variant of adenocarcinoma typically arises in salivary glands, but it is also reported in other sites such as the breast, skin, lung, cervix, larynx, and Bartholin glands (3). Although mammary ACC is histologically similar to ACC arising from other sites, it has a much better prognosis with low rates of axillary lymph node involvement and distant metastases.

There are very few reports in the literature focusing on the imaging features of ACC (3–18). Most of them are case reports. The largest series have been reported by Glazebrook KN and Tang W, both presenting 11 cases (4,5). They have not indicated any specific imaging features for ACC. The purpose of this study is to present our series of 16 ACC lesions

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detected in 13 cases and to review the literature in order to determine the most common imaging features of this tumor.

PATIENTS AND METHODS

A retrospective review of pathological databases of seven institutions from 2009 to 2021 revealed 31 cases of ACC of the breast. All pathological evaluations were performed by dedicated breast pathologists. Thirteen of these cases had radiological studies available in the picture archiving systems (PACS) systems and these 13 cases make up the study population of this study. The researchers and institutions included in this study were all members of the breast imaging working group of the Turkish Society of Radiology.

Clinical information regarding patient age, gender, presenting symptoms, treatment methods, and follow-up data were retrieved from the databases. Two patients who were lost to follow-up were called to check if they had any local or systemic recurrences. Pathological information detailed in the postsurgical pathology reports were recorded.

All radiological studies that were available were recalled from PACS. DICOM images were collected in one center and were re-evaluated by two experienced breast radiologists (with 25 and 10 years of experience) in consensus. Imaging findings were classified according to the Breast Imaging Reporting and Data System (BI-RADS) 5th edition lexicon (19). Lesion type was determined on all imaging modalities as mass or non-mass. Breast density was evaluated from the mammograms. The following morphological features were analyzed for mass lesions. On mammography and digital breast tomosynthesis (DBT): shape, margin, density, associated calcifications; on ultrasound (US) examination: shape, margin, orientation, echo pattern, posterior acoustic features, vascularity and elasticity; on magnetic resonance imaging (MRI): shape, margin, internal enhancement patterns, T2 signal, diffusion characteristics, early and delayed phase kinetic features.

Findings were given as percentages. In order to demonstrate findings more clearly, shape was evaluated as round or oval versus irregular, margins as circumscribed versus non-circumscribed, and BI-RADS category as 3 versus 4 or 5.

The institutional review board of our clinic granted approval for this retrospective study, and patient consent was waived.

RESULTS

All patients were women with a median age of 59 (range 42−73), and all were postmenopausal except one. The presenting symptom was tenderness in one patient, and palpable mass in 7 patients, one of which was painful. The other lesions were detected on screening. Radiological and histopathological evaluation revealed 16 ACC lesions in these 13 patients. Two patients had multifocal lesions (two each), and one had a recurrent tumor. The most common location in the breast was the upper outer quadrant (8/16 lesions). None of them were located in the retroareolar region.

TABLE 1. . Mammographic Features (n:14)

Shape	round/oval	11 (78.57 %)
	irregular	3 (21.43%)
Margin	not circumscribed	9 (64.29 %)
	circumscribed	5 (35.71 %)
Density	dense	10 (71.43 %)
	isodense	4 (28.57 %)
Calcification	none	12 (85.71 %)
	present	2 (14.29 %)
BI-RADS	category 4-5	9 (64.29 %)
	category 3	5 (35.71 %)
Parenchymal density	Type A	0
	Type B	7 (53.84 %)
	Type C	6 (46.15 %)
	Type D	0

There was a second primary breast cancer (invasive ductal carcinoma) in two cases, one of which was a 28 mm lesion located in another quadrant of the same breast. The other was a 5 mm lesion, accompanied by ductal carcinoma in situ (DCIS), located very close to the ACC. It was found incidentally on pathological evaluation of the surgical specimen. Two other patients had accompanying DCIS.

All patients were treated with segmental mastectomy and sentinel lymph node biopsy followed by radiotherapy. Sentinel node was positive in one patient who underwent an axillary lymph node dissection (6/8 lymph nodes positive). The maximum diameter of the lesions ranged between 7 and 36 mm (mean 17.19 mm) on the pathologic specimens. All lesions were either grade 1 or grade 2. Histological subtypes were mostly classical (tubular, cribriform, or mixed). Two cases included < 30% solid component. None displayed skin involvement. Lymphatic and perineural invasion was detected in only one patient who had stage 2 disease (classical subtype) with axillary involvement. This patient had only one breast mass and was not one of those with a second primary breast cancer. Immunohistochemistry analysis revealed that nine lesions were triple-negative, whereas five showed estrogen receptor (ER) (3%−100%), and two showed progesterone receptor (PR) positivity (20% and 70%). None of the lesions displayed Her-2 receptor amplification. Median Ki-67 value was 13% (3%−30%).

There were no distant metastases. Three patients were stage 2 at the time of diagnosis, while the others were stage 1. The patients were followed up for 7−156 months (mean: 68.5 months). Only one patient had local recurrence 145 months after initial diagnosis and underwent total mastectomy. Both the primary and recurrent tumors were of the classical subtype.

Imaging Findings

Mammography and US images of all 16 lesions were available. Five patients also underwent DBT. Seven patients underwent dynamic MRI, one of whom had two lesions. All tumors appeared as mass lesions on all imaging modalities.

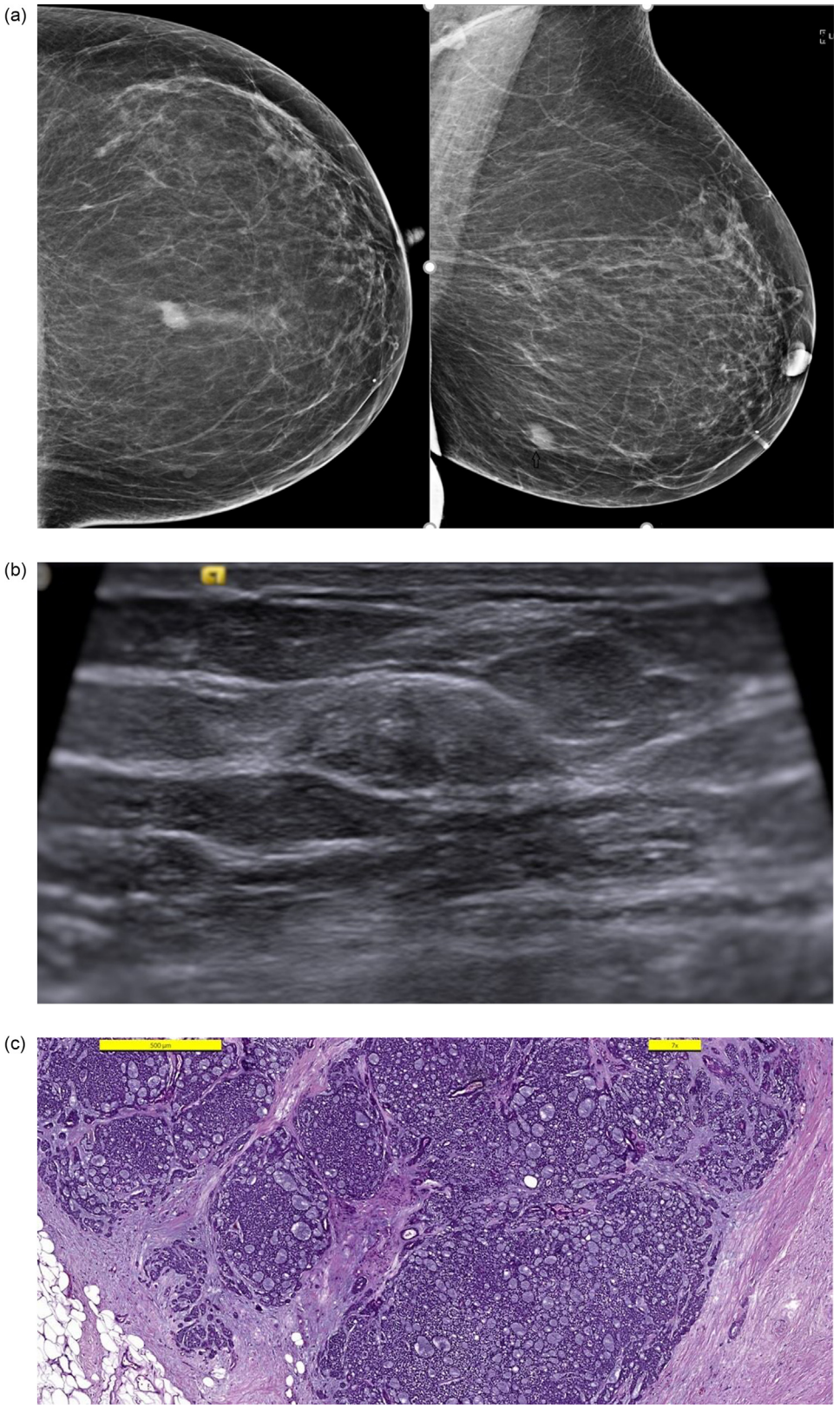


Figure 1. a: 73 y/o female patient: Screening mammograms depict an oval mass with indistict and slightly spiculated margins in the lower inner quadrant of the left breast. Figure 1b:US image shows a heterogeneous iso-hyperechoic solid mass (*arrows)* with partially indistinct margins. Figure 1c: H&E pathologic specimen shows a classical type ACC. Epithelial and myoepithelial cells forming cribriform and tubular structures with mucin in the lumens of tubular structures. (Color version of figure is available online.)

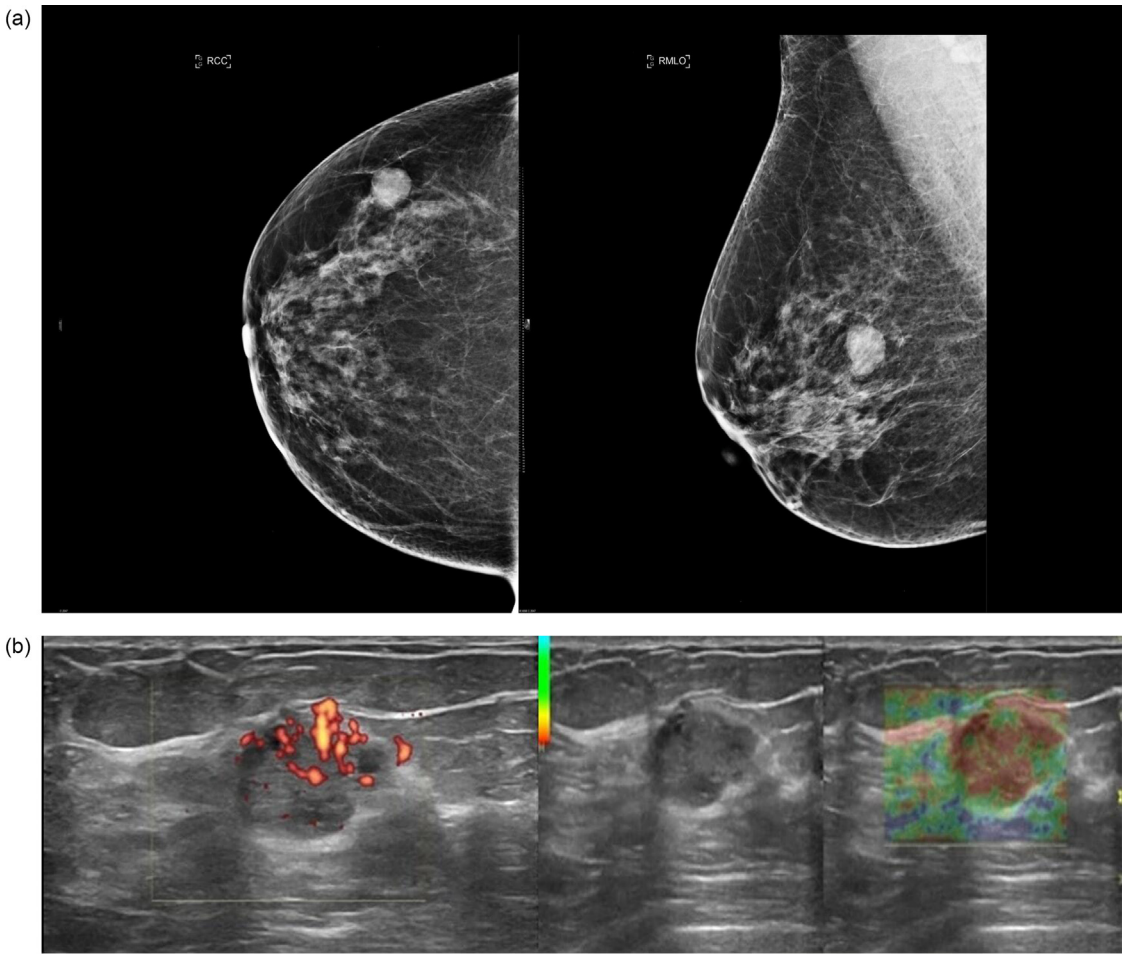


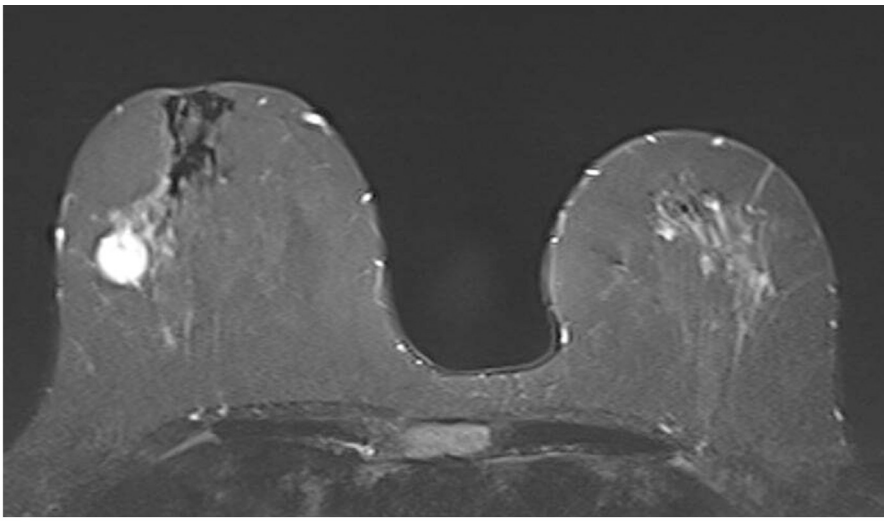
Figure 2. a: 60 y/o patient who presented with a palpable mass in her right breast. Mammograms of the right breast shows a dense round mass with circumscribed margins. Figure 2b: US image (left) demonstrates a round circumscribed isoechoic mass, with internal hypervascularity and posterior acoustic enhancement. The lesion is hard on elastography (right). Figure 2c:On T2 weighted MR image, the lesion is hyperintense. Figure 2d: On contrast-enhanced MR images, there is a thick irregular septa in the mass which enhances in the late contrast enhanced image. (Color version of figure is available online.)

Radiologic sizes of the masses were all concordant with the pathologic size.

Mammography detected 14 masses (Table 1) (Fig. 1–4). Two lesions were not seen due to dense breast parenchyma (type C). The shape was round or oval in 11 masses and irregular in 3. The density of the masses was isodense to fibroglandular tissue in four cases and dense in 10 cases. Margins were circumscribed in four, indistinct in eight, and spiculated in two cases. DBT was available for five of these masses with indistinct margins, and revealed that three of them actually had fine spiculations while one was circumscribed. Few punctate calcifications were present in two of the masses. Based on 2D and 3D mammographic features, five lesions were categorized as BI-RADS 3, while the others were category 4–5. Interestingly one mass could be seen on a mammogram taken 2 years previously in one case. It was not reported at the time, probably because it was partially obscured by the parenchyma. It grew minimally in size but became more dense and distinct over 2 years.

All of the masses could be visualized on US (Table 2) (Fig. 1–5). The orientation of the lesions was parallel in 13 and non-parallel in three. The shape was round or oval in almost all of them, with only one exception which was irregular. The margins were circumscribed in six, and not circumscribed in 10 (indistinct: 5, microlobulated: 2, angular: 1, spiculated: 2). There were no posterior acoustic features in 12 lesions, while four had posterior enhancement. None of the masses displayed posterior acoustic shadowing. The echogenicity was isoechoic or hyperechoic in 10 masses (six of these lesions were heterogeneous), while three were hypoechoic, and three were hypo-anechoic resembling a cyst. Color Doppler US images were available for 12 lesions, six of which were avascular. There was minimal peripheral vascularity in 1 and minimal or increased central vascularity in the other five lesions. Strain elastography findings were available for 4 masses, two of which were soft and the other two were hard. Based on US features, four masses were categorized as BI-RADS 3, and the rest as BI-RADS 4–5.

(c)



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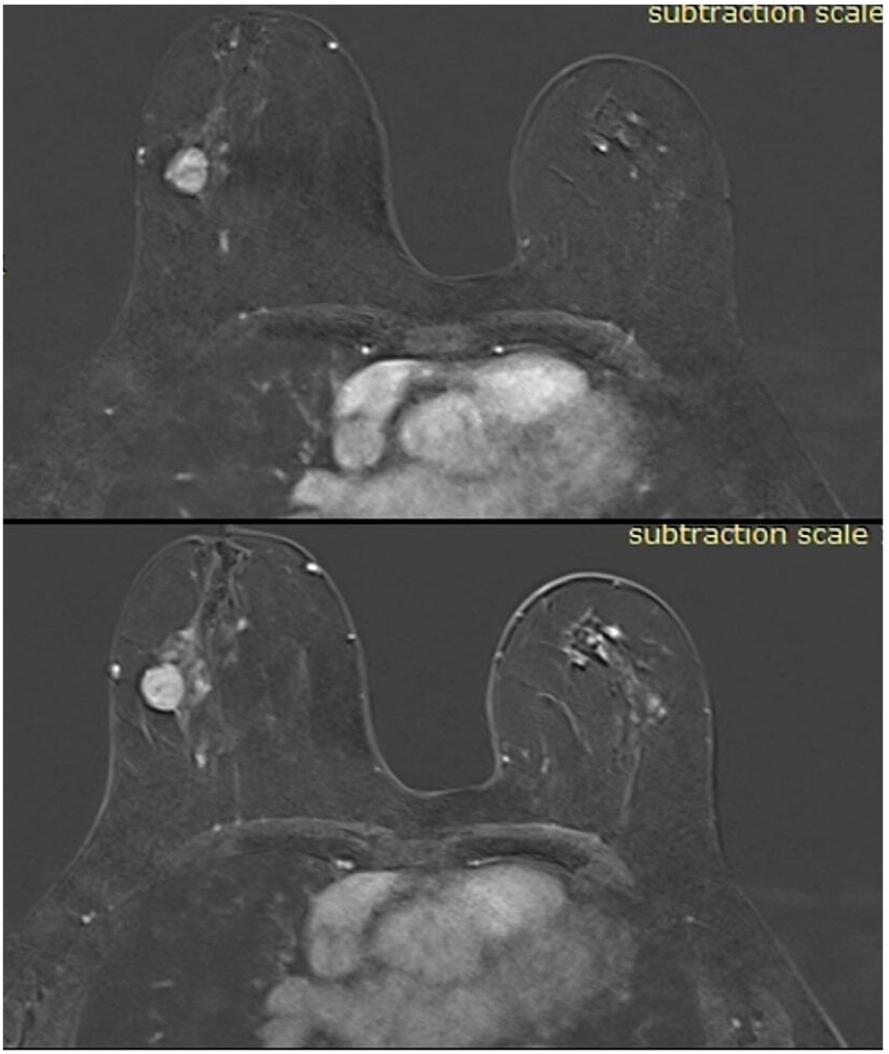

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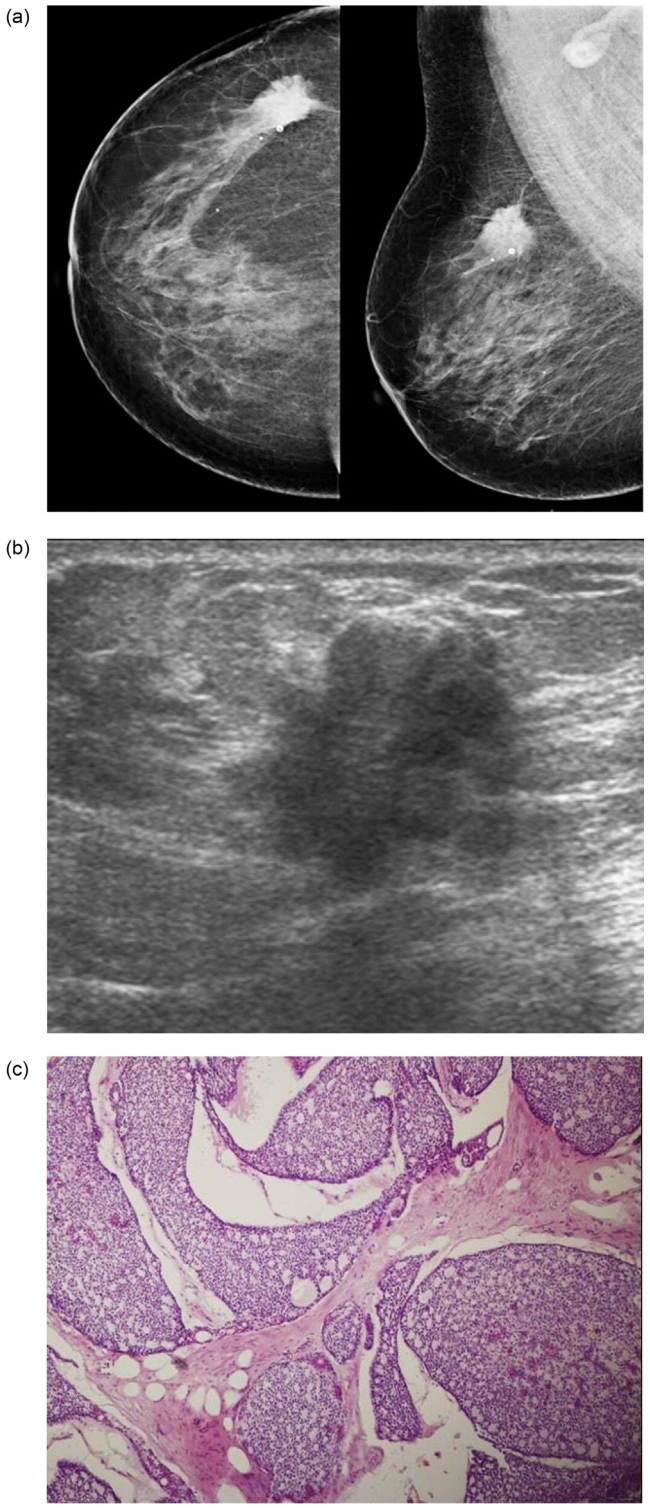

Figure 3. a: 65 y/o patient with a palpable mass in the right breast. Mammograms demonstrate a dense irregular mass with spiculated margins that causes skin retraction in the upper outer quadrant of the right breast. Figure 3b: On US evaluation the lesion is hypoechoic and irregular with spiculated margins (BI-RADS 5). Figure 3c: H and E pathologic specimen shows a cribriform type ACC composed mostly of myoepithelial cells also including epithelial cells. (Color version of figure is available online.)

Dynamic contrast-enhanced breast MRI revealed eight masses in seven patients (Table 3) (Fig. 2,4). The shape was round or oval in all except one. The margins were circumscribed in four, and irregular or spiculated in the rest. Five masses displayed homogeneous enhancement while two had heterogeneous internal enhancement and one displayed rim enhancement. Three cases had an internal septa that enhanced minimally in the late sequences (Fig 2). On T2 weighted images, seven masses were hyperintense and one was hypointense with internal hyperintense foci. On kinetic analysis, all lesions demonstrated more than 100% enhancement in the early phase. The enhancement pattern was persistent or plateau type; and none demonstrated washout kinetics. Diffusion weighted imaging (DWI) was available for seven masses, five of which demonstrated restricted diffusion. Apparent diffusion coefficient (ADC) values were reported only for four masses, and ranged between 0.858 and 1.500×10^{-3} mm^2/s. Based on MRI features, only two masses were evaluated as BI-RADS 3.

When all radiological and clinical findings were evaluated together, none of the lesions were evaluated as BI-RADS 3. Of note, nine lesions were category 4A, signifying the subtlety of malignant findings.

DISCUSSION

In this retrospective study, we have presented the radiological findings of 13 patients with 16 ACC lesions, collected from the databases of seven institutions. This is the largest series in the literature on the radiological findings of this extremely rare type of breast cancer. All patients underwent mammography and US, and seven patients (with eight lesions) underwent MRI. DBT of five lesions were available, while color Doppler US and strain elastography were available in 12 and four lesions respectively. We have reviewed all radiological examinations in detail in order to determine the most common imaging features.

Radiological features of ACC have not been well documented in literature. It is a very rare disease and consequently there are only a few papers on the radiological findings, most of which are case reports. To the best of our knowledge there are only four more comprehensive studies, two of which describe multimodality imaging findings of 11 cases each (4,5), one describes the mammographic features of seven patients (3), and a more recent case series describes the mammography and US findings of five patients (6). In order to provide more detailed and representative information, we decided to do a multicenter study and reviewed all imaging examinations that were available. Besides being the largest series in literature, our study is also the only multicenter study on the radiological features of ACC.

All lesions presented as masses in this study. This is similar to other studies, with few reports describing cases presenting as asymmetry or architectural distortion (3,4). One of the most common radiological features were round or oval shape in all modalities (78.57%–93.75%). Circumscribed margins

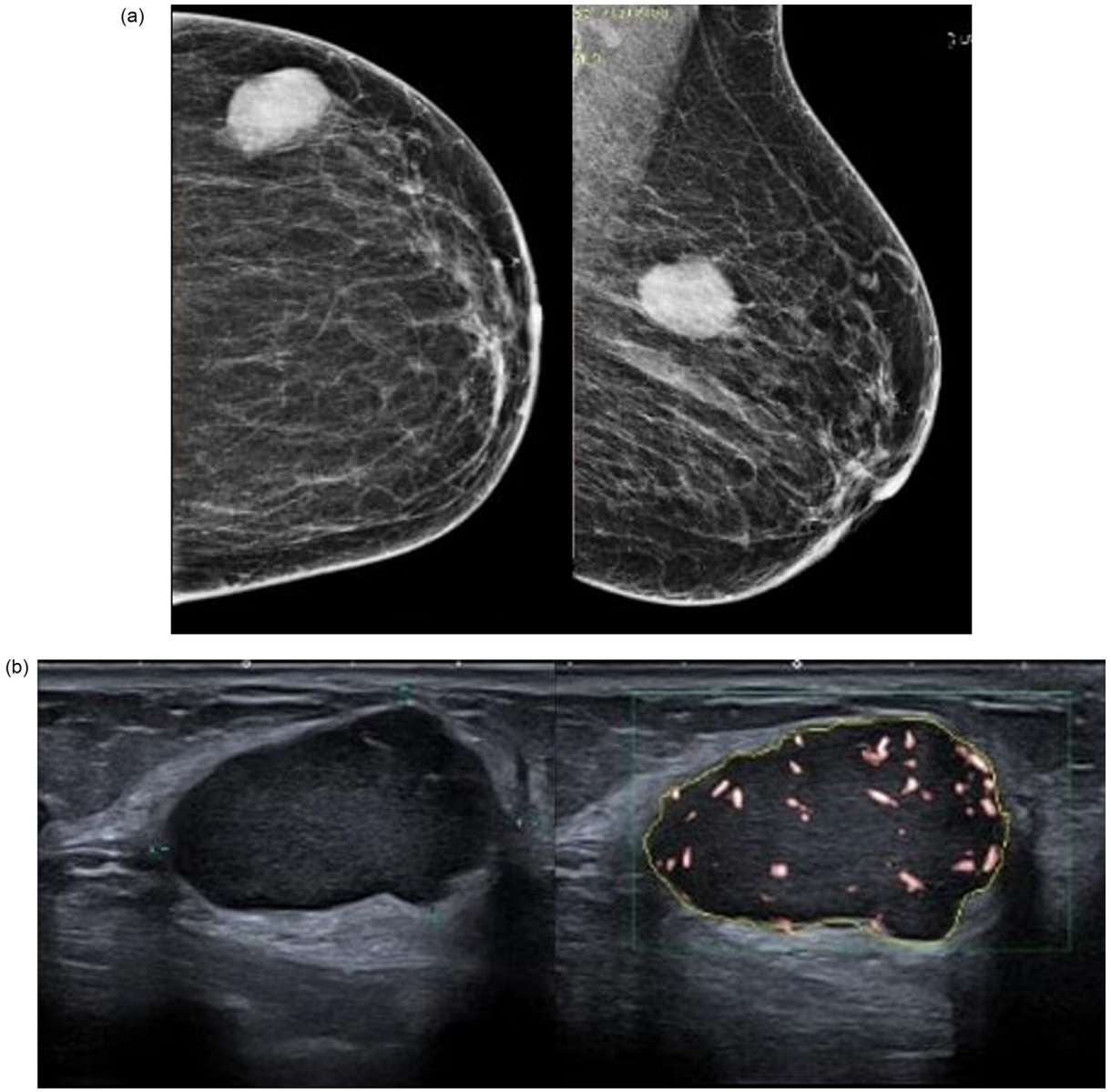

Figure 4. a: 57 y/o female patient with a palpable mass in her left breast. Mammograms show a dense, oval mass with partially indistinct margins in the upper outer quadrant of the left breast. Figure 4b: US demonstrates a circumscribed an anechoic mass resembling a complicated cyst (left); however the lesion has internal hypervascularity on superb microvascular imaging (right). Figure 4c: On T2-weighted MRI (left), the lesion is hyperintense. Significant diffusion restriction is demonstrated on the ADC map in DWI (right). Figure 4d: The lesion has fine spiculations and shows homogeneous intense contrast uptake on the contrast-enhanced axial fat suppressed image from the dynamic series. Figure 4e: H&E pathology specimen (left) shows dual population of luminal and ductal epithelial cells with variable glandular structure. CD117/C kit expression is present in the luminal and ductal epithelial cells (right). (Color version of figure is available online.)

were also relatively common, unlike other histologic types of breast cancer. Circumscribed margins were detected in 35.71% of mammograms, 37.5% of US examinations, and 50% of MRI images. This is contradictory to other series, where most of the lesions were described as lobulated or irregular with non-circumscribed margins on mammograms and US examinations (3–6). Interestingly, lesions were reported to be oval and circumscribed on MRI in the few reports that included MRI findings (5,7,8), with one exception, which reported that all of their cases were irregular (4). Spiculated margins have rarely been reported in the literature (5,9). Similarly only two cases had a spiculated mass on 2D mammography in this study. However, DBT demonstrated fine spiculations in three more cases, which appeared indistinct on 2D mammograms. DBT was helpful in demonstrating margins more clearly in four out of five lesions. In addition to the three cases with spiculations, it revealed circumscribed margins in a mass with indistinct margins on 2D

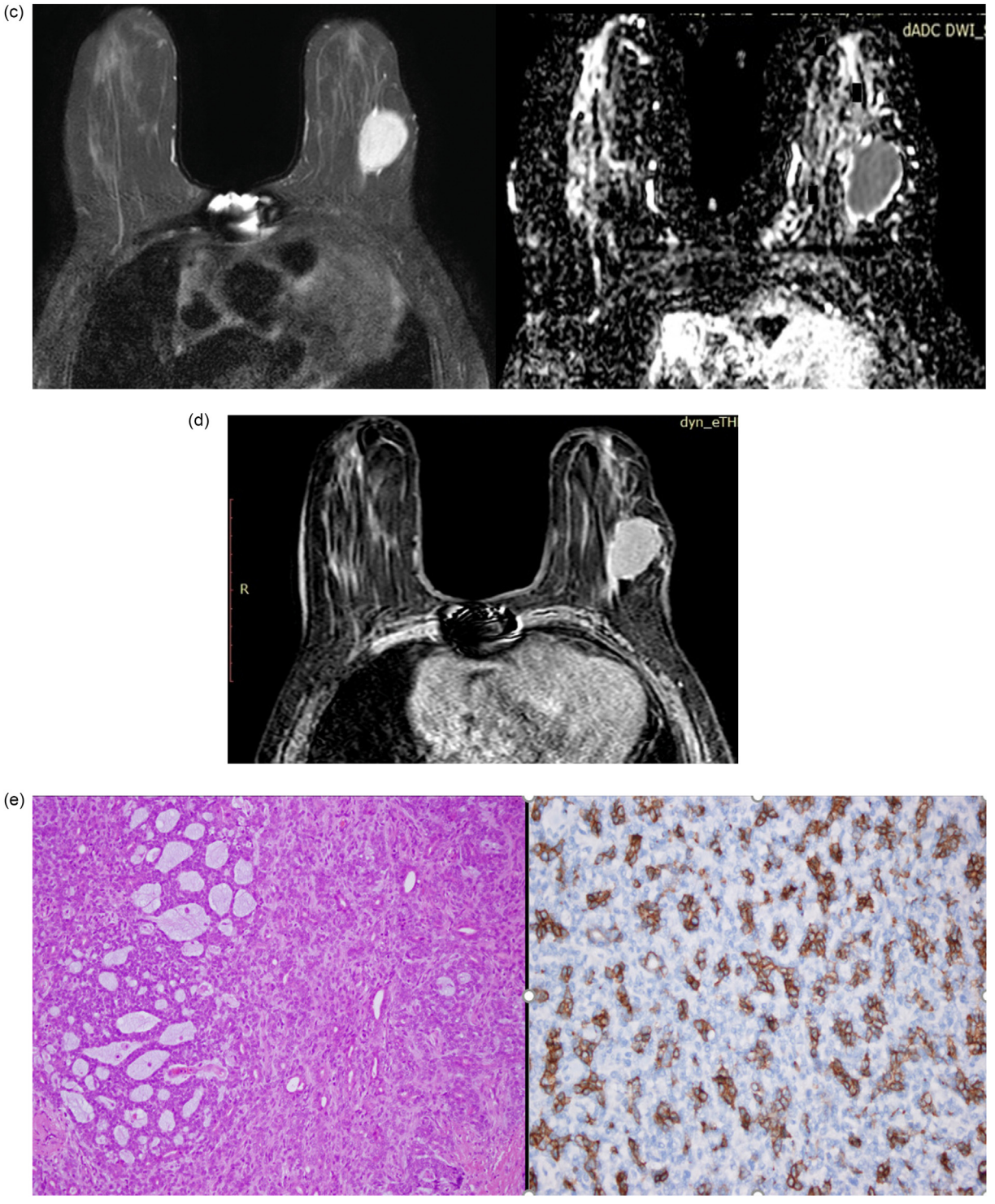

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TABLE 2. US Characteristics (n:16)

Shape	round/oval	15 (93.75 %)
	irregular	1 (6.25 %)
Margin	circumscribed	6 (37.50 %)
	not circumscribed	10 (62.50 %)
Orientation	parallel	13 (81.25 %)
	non-parallel	3 (18.75 %)
Echogenicity	iso/hyperechoic	10 (62.50 %)
	hypoechoic	3 (18.75 %)
	cyst-like	3 (18.75 %)
Posterior features	none	12 (75.00 %)
	enhancement	4 (25.00 %)
Vascularity	vascular	6 (50.00 %)
	non-vascular	6 (50.00 %)
Elasticity	hard	2 (50.00 %)
	soft	2 (50.00 %)
BI-RADS	category 4-5	12 (75.00 %)
	category 3	4 (25.00 %)

mammography. Calcifications are extremely rare in ACC. It has been described in only one case series (3). Few punctate calcifications were present in two cases in this study.

Another striking finding in our series was the echogenicity on US. Ten out of 16 masses (62.5%) were either isoechoic or hyperechoic (Fig 1−3). Six of these lesions were heterogeneous and had both isoechoic and hyperechoic components within. This finding has not been mentioned in any of the previous papers, which have reported lesions to be generally either hypoechoic or heterogeneous, although some images included in some series do seem similar to our cases (4,5,10). This finding is important, because classic echogenicity of breast cancer on US is hypoechoic. Isoechoic and hyperechoic lesions are atypical, and tend to be regarded mostly as benign. Moreover, they can be easily overlooked, because they can appear similar to fat lobules. Mucinous breast cancer, another rare form of malignancy in the breast, can have a similar appearance. Interestingly three masses showed very low echogenicity, almost anechoic, resembling a complicated cyst. Low echogenicty has been described in some high grade breast cancers, but it has not been reported in ACC previously. It may be another reason for some ACC lesions to be missed on routine US examinations. Only three masses had the classic echogenicity (hypoechoic) of breast cancers in this series.

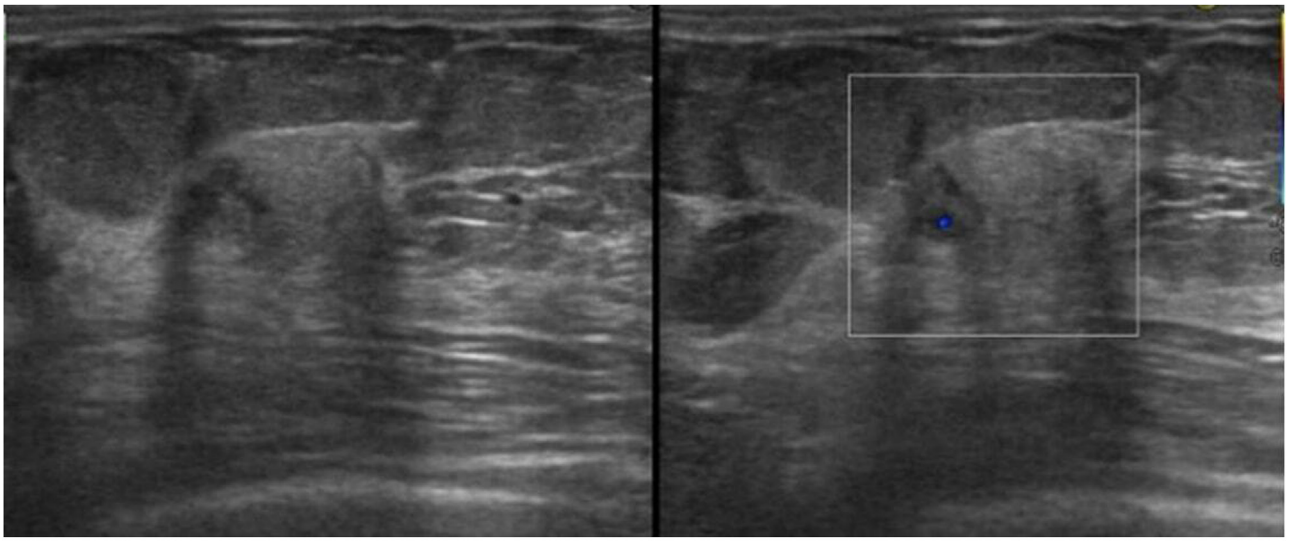
There were no specific findings regarding color Doppler US and sonoelastography. On color Doppler US, 50% of the cases (6/12) were avascular, while the other half demonstrated minimal to enhanced vascularity. Strain elastography was available in only four cases, two of which were hard while the other two were soft. Huang M et al. have first described the shearwave elastography findings in a case report, in which the stiffness was increased in the surrounding parenchma (11). Elastography findings were not mentioned in other reports to the best of our knowledge.

Posterior shadowing on US examination, another typical feature for malignancy, is very rare in ACC. It has been described only in two case reports previously (12,13). We did not detect posterior shadowing in any of the cases in this study. Most lesions did not demonstrate any posterior acoustic features, while 4 showed enhancement, in accordance with literature (11,14). Most lesions (13/16 − 81.25%) had parallel orientation on US, which is again a finding more typical for a benign lesion.

The most typical finding on MRI was the high T2 signal. Seven out of eight masses (87.5%) demonstrated moderate to extensive high signal intensity, while the other lesion was isointense but had hyperintense foci within. This finding has also been described in the two series that included MRI findings (4,5). High intensity on T2 weighted images is typical for benign lesions, mostly fibroadenomas, and also some rare malignancies such as mucinous tumors. Glazebrook et al have described internal septations on MRI. We had three cases which had thin or thick septae that enhanced in the late sequences. None of the cases demonstrated washout kinetics in our study, which is also rare in other series (4,5,7). DWI showed showed restricted diffusion in five out of seven lesions. Restricted diffusion was helpful in characterizing ACC lesions on MRI, because the other features mostly resembled benign lesions.

We have categorized findings as BI-RADS 3 in 35.71% (5/14) of the cases in mammography, and in 25% of the cases in US and MRI (4/16 and 2/8 cases respectively). When all imaging findings were taken into account none of the lesions were considered BI-RADS 3. However, it should be noted that only one mass was considered BI-RADS 5, while 9/16 masses were BI-RADS 4A. This emphasizes the subtle nature of malignant features in ACC. Because of this, lesions can be overlooked or misdiagnosed especially on US and mammography, as has also been pointed out by Sheen Chen et al (10). Other series in the literature have described imaging findings as BIRADS 4 or BI-RADS 5 (4−6), although there are some reports describing lesions with benign features (7,10).

ACC is more common in postmenopausal women. It can present with pain and this may be a clue for diagnosis (10,20). Only two patients had pain in this study. Multifocality is very rare (15,21). We had two patients with multifocal lesions. Local recurrence is reported to be around 3%−18% (22), but multiple recurrences have been reported in one case (4). Although most cases are triple negative, prognosis is excellent. Arpino et al. and Kulkarni et al have reported axillary involvement rate as 1.7% and 5% respectively (23,24). Distant metastases are very rare, reported to be 7.6% (23). It can occur in the absence of lymph node involvement with the lung being the most common site of metastasis (1). We had only one patient with positive axillary lymph nodes, and another patient with local recurrence, which was detected by screening 145 months after therapy. There were no distant metastases. It has been reported that the lesions grow slowly, and there are some cases that have been stable for years in the literature (3,4,15,21). One of the masses in our study was present in a screening mammogram taken 2 years previously, showing minimal increase in size. Some authors believe that



a

b

Figure 5. a: 56 y/o woman with dense breasts on screening mammography (not shown), which did not show any lesion. On screening US examination, a hyperechoic heterogeneous solid mass with indistinct margins was detected which showed minimal internal vascularity on Doppler imaging. Figure 5b: 56 y/o woman who presented with a palpable mass in her right breast. US image demonstrates two masses which resemble complicated cysts. (Color version of figure is available online.)

size is an important prognostic factor and larger lesions are more prone to metastases (25,26). The tumor sizes in literature vary between 0.4 and 10 cm (mean size 3 cm) (23,27). The mean tumor size was around 1.7 cm in this study. Grade is another important factor for prognosis. None of the lesions were grade 3, which is characterized by a solid component of more than 30%. Gabach et al did not find an increased risk for breast cancer preceding or following breast ACC (2). However, there was a synchronous invasive ductal carcinoma in two cases in this study, and DCIS was present in three cases on histologic specimens.

The major limitation of this study is the low number of cases. However ACC is a very rare tumor, and it is the largest series in the literature on imaging findings. Another important limitation is the retrospective nature of the study. Although there were more patients with a diagnosis of ACC, the radiological examinations could not be accessed retrospectively in all of them, and some examinations were not performed in some cases. Moreover, retrospective evaluation of radiological findings, especially US findings, can be misleading. We did correlate our findings with the original US reports, and they were concordant, however some features

TABLE 3. MRI Features (n:8)

Shape	round/oval	7 (87.50 %)
	irregular	1 (12.50 %)
Margin	circumscribed	4 (50.00 %)
	not circumscribed	4 (50.00 %)
T2 signal	hyperintense	7 (87.50 %)
	isointense	1 (12.50 %)
Internal Enhancement	homogenous	5 (62.50 %)
	heterogenous	2 (25.00 %)
	rim	1 (12.50 %)
Enhancement Kinetics	plateau	6 (75.00 %)
	persistent	2 (25.00 %)
DWI (n = 7)	restricted	5 (71.43 %)
	non-restricted	2 (28.57 %)
BI-RADS	category 4-5	6 (75.00 %)
	category 3	2 (25.00 %)

were not recorded in the reports. On the other hand, this is a multicenter study and it is the only multimodality study with detailed evaluation of all BI-RADS features.

In conclusion, ACC of the breast is a very rare, slow growing tumor with good prognosis, diagnosed more commonly in postmenopausal women. The imaging features may mimick a benign lesion on all imaging modalities. In this study, the most common findings were round or oval shape on all modalities, isoechoic or hyperechoic echogenicity and parallel orientation on US, high T2 signal and restricted diffusion on MRI. Some classic findings of breast cancers such as calcifications, posterior shadowing, non parallel orientation, and washout kinetics are very rare in ACC. US findings of isoechoic or hyperechoic appearance, and cyst-like echogenicity have not been reported previously in literature. Although combination of all imaging findings correctly indicated the suspicious nature of the lesions in all cases, final classification was BI-RADS 4A in nine out of 16 lesions, emphasizing the subtlety of malignant findings and the importance of multimodality evaluation. Radiologists should be aware of the more frequent findings of ACC of the breast in order to detect them early, since larger size has been associated with distant metastases.

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