Chapter

Correlation between Ultrasound Findings and Molecular Subtypes of Breast Cancer

Eman Soliman Metwally, Rahma Mohammed Abed Alghazal and Ah Haggaa Ali

Abstract

Breast cancer is the most common malignant tumor and the major cause of death among women worldwide. Molecular subtyping of breast cancer is important to individualize its management, to understand prognosis of disease and avoid overtreatment. The current study aimed at correlating the breast cancer subtypes with their different ultrasound criteria. The ultrasound findings might have an important role in predicting different groups. The current study is a retrospective study. Which was conducted on 40 females patients with breast cancer; during the period from November 2020 till March 2021.The age were 45–65 years old. They were presented to the Radiology Department, ·Ain-Shams University, Faculty of Medicine. The selected cases had been afforded from: the Breast-unit of General Surgery Hospital, El Demerdash University Hospital, Clinical Oncology & Nuclear Medicine Department. When analyzing the main four breast cancer subtypes in the current work we found that the rates of Luminal A was 34%, Luminal B was 40%, HER2 was 15%, and TNBC was 11%. LA subtype was strongly associated with hypoechoic lesions showing irregular shape, speculated margin surrounded by desmoplastic reaction with posterior shadowing. LB subtype was associated with irregular shape and speculated margin with absence of desmoplastic reaction. Human Epidermal Growth Factor (HER2) subtype in the current study was found to be associated with irregular shape, lobulated margin, absent desmoplastic reaction with posterior acoustic mixed shadowing and enhancement. This could be related to suspicious microcalcifications. Triple Negative Breast Cancer (TNBC) lesions in the present work were predominantly oval in shape with• circumscribed margin; the benign looking malignant lesions which carry the worst prognosis. Based on the latter finding, the good radiologist should be aware about ultround features of different molecular subtype in order not to under diagnose a malignant breast lesion. The sonographic features as margin, shape, posterior acoustic features were significantly associated with molecular subtypes. The histopathological grade and hormone receptor status. Being able to predict the molecular subtype. The current study recommend that the radiologist should be aware about different imaging features of different molecular subtypes especially the triple negative breast cancer which had the most benign looking criteria aiming for better lesion characterization and to allow the patient to benefit from earlier non-invasive, cheap diagnosis and the curable on time treatment.

Keywords: breast cancer, ultrasound features, molecular subtypes

1. Introduction

Cancer Breast is a heterogeneous and complex disease with different morphologic, biologic, and molecular features. The histopathological characteristics of tumors had been used to determine the management of breast cancer. However They do not provide sufficient information due to tumor heterogeneity [1–3].

Distinct molecular subtypes of breast cancer had been defined based on gene expression. Molecular subtyping of breast cancer is essential to individualize its management, to understand prognosis of disease and avoid overtreatment [4].

Ultrasonographic imaging features of breast cancer, including the tumor shape, margin, boundaries, posterior features, multiplicity, orientation, and calcification, are significant predictive sonographic signs of different molecular subtypes [5].

Previous literatures had indicated an excellent improvement in U/S technologies. It would be possible to have highly sensitive machines be able to differentiate malignant solid breast masses from benign ones based on their different U/S criteria [6].

Many studies correlated the ultrasonography features of malignant lesions with their grade, while limited studies discussed the correlation with molecular subtypes of breast cancer. Overlap of benign and malignant ultrasound morphology descriptors still represents a challenge to breast imaging radiologists. Knowing the descriptors of the different molecular subtypes may help radiologists to decrease both false positive and false negative diagnosis [3–6].

2. Aim of the work

The present study aimed at detecting the correlation between ultrasound morphological features and different molecular subtypes of breast cancer which could increase the diagnostic ultrasound accuracy.

3. Patients and methods

The current study is a retrospective study. Which was conducted on females patients with breast cancer. They were presented to the Radiology Department, Ain-Shams University, Faculty of Medicine. The selected cases had been afforded from: The Breast-unit of General Surgery Hospital, El Demerdash University Hospital, Clinical Oncology & Nuclear Medicine Department.

- Number of patients: 40 female patients had breast cancer.
- Time: during the period from November 2020 till March 2021.
- Age: 45–65 years old ±10.58.

An informed consent explaining the procedure details was obtained from all patients prior to inclusion in this study. The study was conducted according to the stipulations of the ASU ethical and scientific committee. The privacy of participants and confidentiality of data were guaranteed during the various phases of the study. The inclusion criteria were: Female patients with breast cancer, only. The exclusion Criteria were: a) History of neoadjuvant therapy; b) Ductal carcinoma in situ; c) Patients had started any local or systemic therapy.

3.1 Study methods

Forty female patients had breast cancers were selected for the present study the inpatient wards as well as outpatient clinic were admitted for bilateral Sonomammographic examination. An U/S device; GE (Pristima), Siemens (Mammomat 1000) & Samsung (Accuvix XG) machines in Ain Shams University Medical Hospital. A linear probe of 9–15 MHz was used.

The technique was done after exposure of the breast with the patient lying supine and her ipsilateral hand raised above the head the UIS probe was oriented perpendicular to the chest wall. Radial scanning technique, in a clockwise fashion wising the nipple as a center point wall followed. Scanning of each breast quadrant in the sagittal and transverse planers were performed. Scanning axially lymph nodes.

The examination time took about 20 minutes. All the real-time scanning was performed by a radiologist with at least 5 years of experience in breast U/S. More experienced radiologist with at least 7–10 years' experience rechecked the findings. As a way of a double-blind analysis. The final interpretation and diagnosis were obtained.

3.2 Histopathologic diagnosis, image analysis and interpretation of conventional ultrasound

U/S guided biopsy was scheduled for patients with suspicious breast lesions. The procedure was performed by at least 7–10 years experienced radiologist. Biopsy was taken under complete aseptic condition. Sterilization of the area of interest with betadine was done; the latter was followed by sterilization the U/S probe. The radiologist used sterile gloves and injected a local anesthesia followed by introduction of the Tru-cut needle. The needle under ultrasound guidance targeted the lesion. At least four core biopsies were taken.

Tissues biopsied were sent to the Pathology Department. The tissues were formalin fixed, paraffin embedded and subsequently used for IHC staining with appropriate antibodies to detect the hormonal status of the lesions (ER, PR, HER2 gene expression and Ki-67). The cutoff point for ER positive, PR-positive expression was 10%. HER-2 status was graded as 0, 1+, 2+ and 3+. The HER-2 status of 3+ was deemed to be positive, while statuses of O and 1+ were deemed to be negative. Fluorescence in situ hybridization (FISH) was performed on all grade 2 samples. Samples with a > 2-frold-change in expression were regarded as negative. Samples with a < 2-fold increase were regarded as positive for gene amplification. Ki67 was visually scored for the percentage of tumor cell nuclei with positive immunostaining above background. Over **Histopathologic diagnosis** by following and receiving the pathology report from the patient.

3.3 Statistical analysis

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean ± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done: Chi-square (x^2) test of significance was used in order to compare proportions between qualitative parameters. The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the· following: - Probability (P-value). P-value $\leq$0.05 was considered significant. P-value $\leq$0.001 was considered as highly significant. P-value >0.05 was considered insignificant.

4. Results

The current study comprised 40 female patients with cancer breast. The resulting analysis of the main four breast cancer subtypes of the current work among the patients showed the following figures:

- LA: 34% i.e. 14 patients.
- LB: 40% i.e. 16 patients.
- TNBC: 11% i.e. 4 patients.
- HER2: 15% i.e. 6 patients (**Tables 1**–5).

		n	Row%	Column %	P value
Age groups	<=50 yrs	8	33.3%	55.9%	
	>50 yrs	6	34.9%	44.1%	0.429
Density	Fatty	8	33.9%	55.9%	
	Fibroglandular	6	34.1%	44.1%	0.832
Shape	Oval	2	15.4%	11.8%	
	Irregular	12	40.5%	88.2%	<0.001
Margin	Circumscribed	2	13.3%	5.9%	
	Lobulated	4	20.0%	17.6%	
	Speculated	8	47.3%	76.5%	
Echogenicity	Hyper				
	Iso	2	27.8%	14.7%	
	Hypo	12	35.4%	85.3%	0.713
E	Enhancement	2	18.2%	11.8%	
S	Shadowing	10	51.1%	70.6%	
M	Mixed	2	19.4%	17.6%	
Number of	Single	10	33.8%	64.7%	
Lesion	Multiple	4	34.3%	35.3%	0.219
Calcification	No	8	30.6%	55.9%	
	Yes	6	39.5%	44.1%	0.025

		n	Row%	Column %	P value
Size grouped	<2	10	38.3%	52.9%	
	> = 2	4	30.2%	47.1%	0.036
Surrounding	No	10	32.4%	67.6%	
Parenchyma	Yes	4	37.9%	32.4%	0.613
Desmoplastic reaction	No	5	22.1%	44.1%	
	Yes	9	59.4%	55.9%	<0.001

Table 1.
Showing age, U/S criteria of LA subtype.

		N	Row %	Column %	P value
Age groups	<=50 yrs	10	40.4%	60.5%	
	>50 yrs	6	34.9%	39.5%	0.429
Density	Fatty	10	41.1%	60.5%	
	Fibroglandular	6	34.1%	39.5%	0.832
Shape	Oval	5	34.6%	23.7%	
	Irregular	11	39.2%	76.3%	<0.001
Margin	Circumscribed	2	40.0%	15.8%	
	Lobulated	4	33.3%	26.3%	
	Speculated	10	40.0%	57.9%	
Echogenicity	Hyper				
	Iso	2	33.3%	15.8%	
	Hypo	14	39.0%	84.2%	0.713
E	Enhancement	2	36.4%	21.1%	
S	Shadowing	10	34.0%	42.1%	
M	Mixed	4	45.2%	36.8%	
Number of	Single	14	38.5%	65.8%	
Lesion	Multiple	2	37.1%	34.2%	0.219
Calcification	No	11	46.8%	76.3%	
	Yes	5	23.7%	23.7%	0.025
Size grouped	<2	8	40.4%	50.0%	
	> = 2	8	35.8%	50.0%	0.036
Surrounding	No	11	40.8%	76.3%	
parenchyma	Yes	5	31.0%	23.7%	0.613
Desmoplastic	No	10	41.2%	73.7%	
Reaction	Yes	6	31.3%	26.3%	<0.001

Table 2.
Showing age, U/S criteria of LB subtype.

		n	Row %	Column %	P value
Age groups	<=50 yrs	1	15.8%	69.2%	
	>50 yrs	3	9.3%	30.8%	0.429
Density	Fatty	2	10.7%	46.2%	
	Fibroglandular	2	15.9%	53.8%	0.832
Shape	Oval	3	34.6%	69.2%	
	Irregular	1	5.4%	30.8%	<0.001
Margin	Circumscribed	3	46.7%	53.8%	
	Lobulated	0	13.3%	30.8%	
	Speculated	1	3.6%	15.4%	
Echogenicity	Hyper				
	Iso	1	16.7%	23.1%	
	Hypo	3	12.2%	76.9%	0.713
E	Enhancement	2	31.8%	53.8%	
S	Shadowing	1	6.4%	23.1%	
M	Mixed	1	9.7%	23.1%	
Number of	Single	4	16.9%	84.6%	
lesion	Multiple	0	5.7%	15.4%	0.219
Calcification	No	3	14.5%	69.2%	
	Yes	1	10.5%	30.8%	0.025
Size grouped	<2	3	17.0%	61.5%	
	>=2	1	9.4%	38.5%	0.036
Surrounding	No	4	14.1%	76.9%	
parenchyma	Yes	0	10.3%	23.1%	0.613
Desmoplastic	No	4	17.6%	92.3%	
reaction	Yes	0	3.1%	7.7%	<0.001

Table 3.
Showing age, U/S criteria of TNBC subtype.

		n	Row %	Column %	P value
Age groups	<=50 yrs		15.8%	69.2%	
	>50 yrs	9	9.3%	30.8%	0.429
Density	Fatty	8	10.7%	46.2%	
	Fibroglandular	7	15.9%	53.8%	0.832
Shape	Oval	4	34.6%	69.2%	
	Irregular	11	5.4%	30.8%	<0.001
Margin	Circumscribed	0	46.7%	53.8%	
	Lobulated	10	13.3%	30.8%	
	speculated	5	3.6%	15.4%	

		n	Row %	Column %	P value
Echogenicity	Hyper				
	Iso	4	16.7%	23.1%	
	Hypo	11	12.2%	76.9%	0.713
E	Enhancement	3	31.8%	53.8%	
S	Shadowing	4	6.4%	23.1%	
M	Mixed	8	9.7%	23.1%	
Number of	Single	7	16.9%	84.6%	
lesion	Multiple	8	5.7%	15.4%	0.219
Calcification	No	5	14.5%	69.2%	
	Yes	10	10.5%	30.8%	0.025
Size grouped	<2	2	17.0%	61.5%	
	>=2	13	9.4%	38.5%	0.036
Surrounding	No	9	14.1%	76.9%	
parenchyma	Yes	6	10.3%	23.1%	0.613
Desmoplastic	No	13	17.6%	92.3%	
reaction	Yes	2	3.1%	7.7%	<0.001

Table 4.
Showing age, U/S criteria of HER2 subtype.

		n	Row%	Column%	P value
LA subtype: For 14 patients					
Pathology	IDC	12	29.9%	76.5%	
	ILC	2	61.5%	23.5%	
Grade	1	12	43.9%	73.5%	
Grouped	2	2	20.9%	26.5%	0.050
		n	**Row%**	**Column%**	**P value**
LB subtype: For 16 patients					
Pathology	IDC	38	39.1%	89.5%	
	ILC	2	30.8%	10.5%	
Grade	1	22	35.1%	52.6%	
Grouped	2	18	41.9%	47.4%	0.050
		n	**Row%**	**Column%**	**P value**
TNBC subtype: For 4 patients					
Pathology	IDC	3	13.8%	92.3%	
	ILC	1	7.7%	7.7%	
Grade	1	1	7.0%	30.8%	
Grouped	2	3	20.9%	69.2%	0.050

		n	Row%	Column %	P value
HER2 subtype: For 6 patients					
Pathology	IDC	6	17.2%	100.0%	
	ILC	0	0.0%	0.0%	
Grade	1	4	14.0%	53.3%	
Grouped	2	2	16.3%	46.7%	0.05

Table 5.
Showing the histopathological results and grade in different molecular subtypes.

4.1 Luminal A breast cancer case presentation

52-year-old female patient presented, symptomless, was imaged for screening. Family history of breast cancer: positive (**Figure 1**).

Histopathological examination result:

Invasive ductal carcinoma grade II.

Immunohistochemical revealed:

ER: positive
PR: positive
HER2: negative
Ki-67: 2%

4.2 Luminal B HER2 –ve breast cancer case presentation

58-year-old female patient presented with right breast lump. Family history: Negative (**Figure 2**).

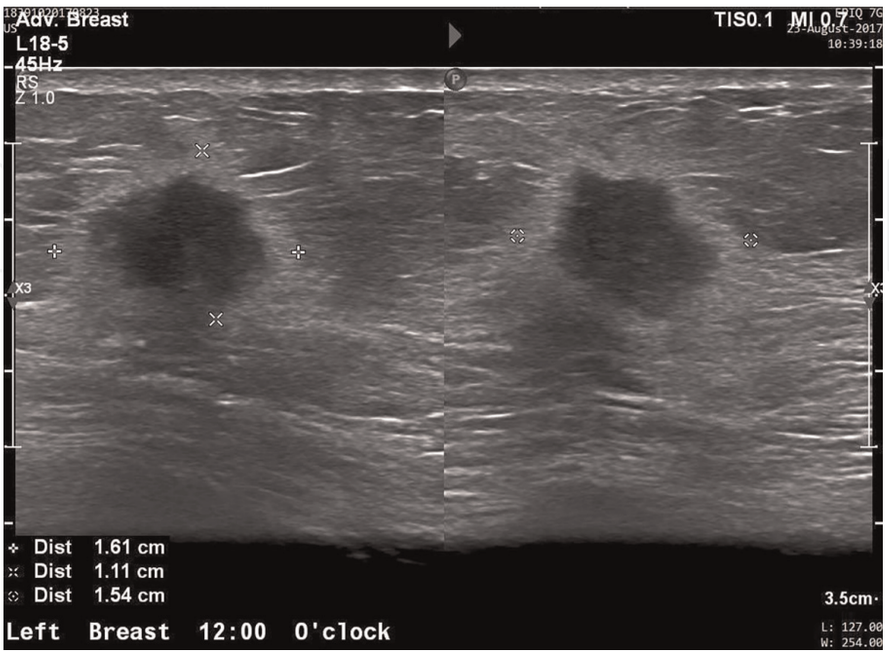

Figure 1.
U/S showing hypoechoic lesion, irregular in shape with spiculated margin, measuring 1.6x1.1 cm in its maximum dimensions surrounded by desmoplastic reaction and showing posterior acoustic shadowing.

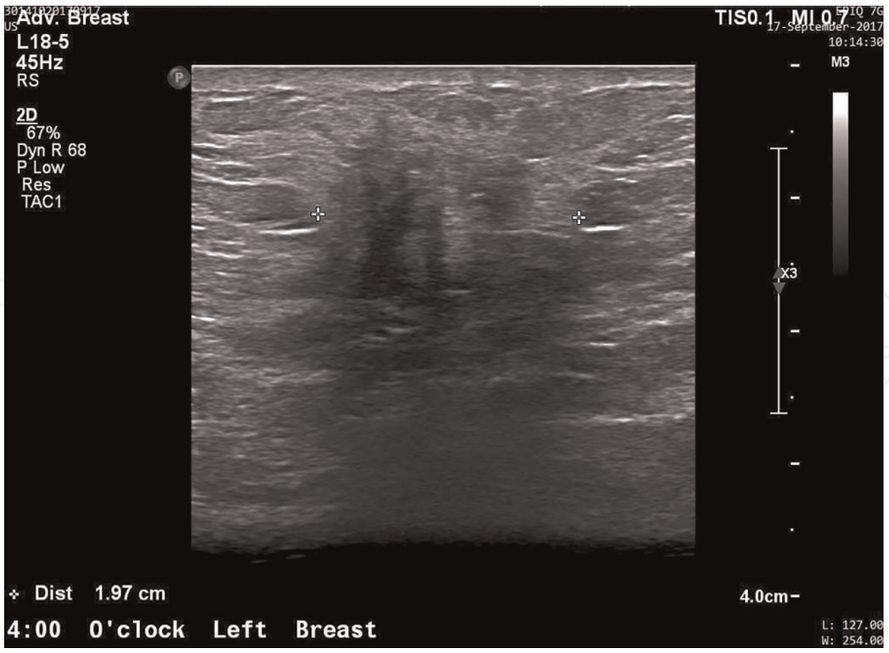

Figure 2.
U/S of fibroglandular breast showing hypoechoic irregular lesion with speculated margin, measuring 2 cm in its maximum dimension not surrounded by desmoplastic reaction with posterior acoustic shadowing. The parenchyma showed mild distortion.

Histopathological examination result:
Invasive ductal carcinoma grade II

Immunohistochemistry revealed:
ER: positive
PR: negative
HER2: negative
Ki-67: 50%

4.3 Luminal B HER2 –ve breast cancer case presentation

65-year-old female patient presented with right breast mass. Family history: Positive (**Figure 3**).

Histopathological examination result:
Invasive duct carcinoma grade II

Immunohistochemistry revealed:
ER: positive
PR: negative
HER2: negative
Ki-67: 50%

4.4 Luminal B HER2 ±ve breast cancer case presentation

60-years-old female patient presented with left breast lump. Family history: Negative (**Figure 4**).

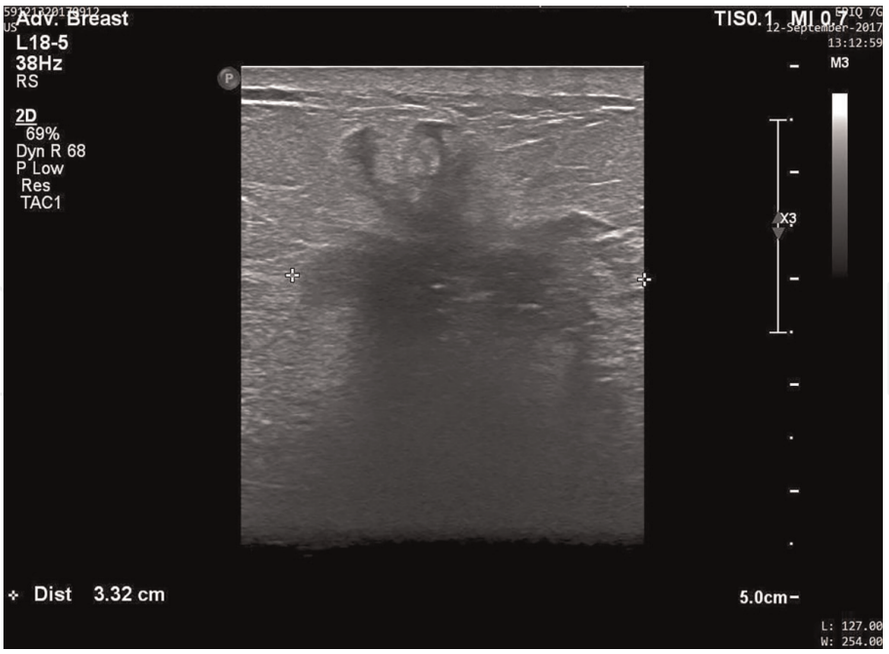

Figure 3.
U/S breast showing irregular shaped lesion with speculated margin measuring 3.3 cm in its maximum dimension showing posterior acoustic shadowing.

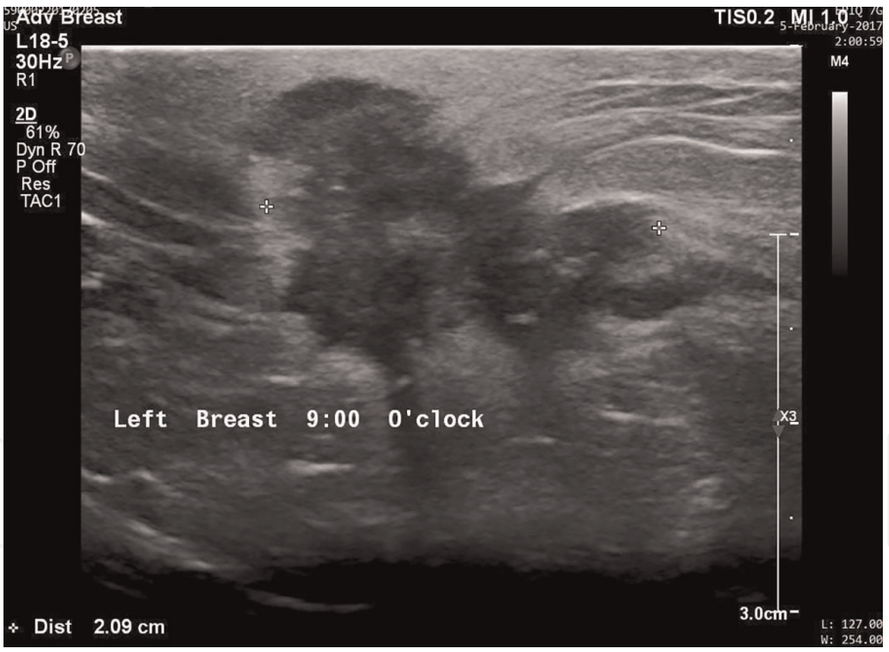

Figure 4.
U/S of fibroglandular breast showing hypoechoic focal lesion, irregular in shape with speculated margin and not surrounded by desmoplastic reaction, mixed posterior acoustic shadowing and enhancement. The parenchyma showed distortion and few calcific foci.

Histopathological examination result:
Invasive duct carcinoma grade III

Immunohistochemical results revealed:
ER: positive
PR: negative

HER2: positive
Ki-67: 30%

4.5 Triple negative breast cancer case presentation

47-years-old female patient presented with left breast mass. Family history: Negative (**Figure 5**).

Histopathological examination result:
Invasive ductal carcinoma grade III.

Immunohistochemistry results:
ER: negative
PR: negative
HER2: negative
Ki-67: 30%

4.6 Triple negative breast cancer case presentation

45-year-old female patient presented with right breast mass. Family history: Negative (**Figure 6**).

Histopathological examination result:
Invasive ductal carcinoma grade III.

Immunohistochemistry results:
ER: negative
PR: negative
HER2: negative
Ki-67: 50%

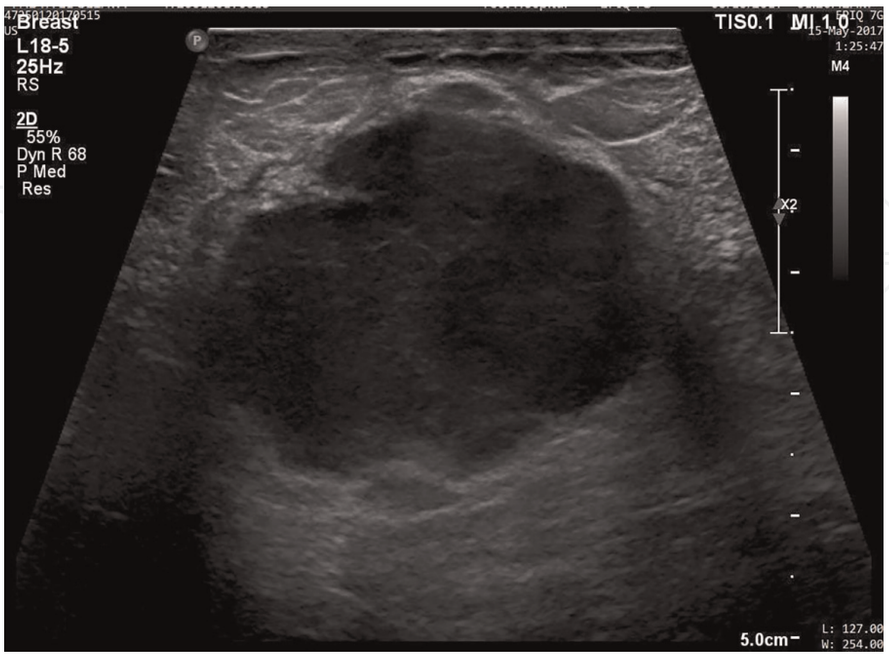

Figure 5.
U/S showed fibroglandular breast with hypoechoic oval shaped lesion with circumscribed margin, measuring 4.3x3.6 cm in its maximum dimensions showing posterior acoustic enhancement with edge attenuation. The lesion is not surrounded by desmoplastic reaction.

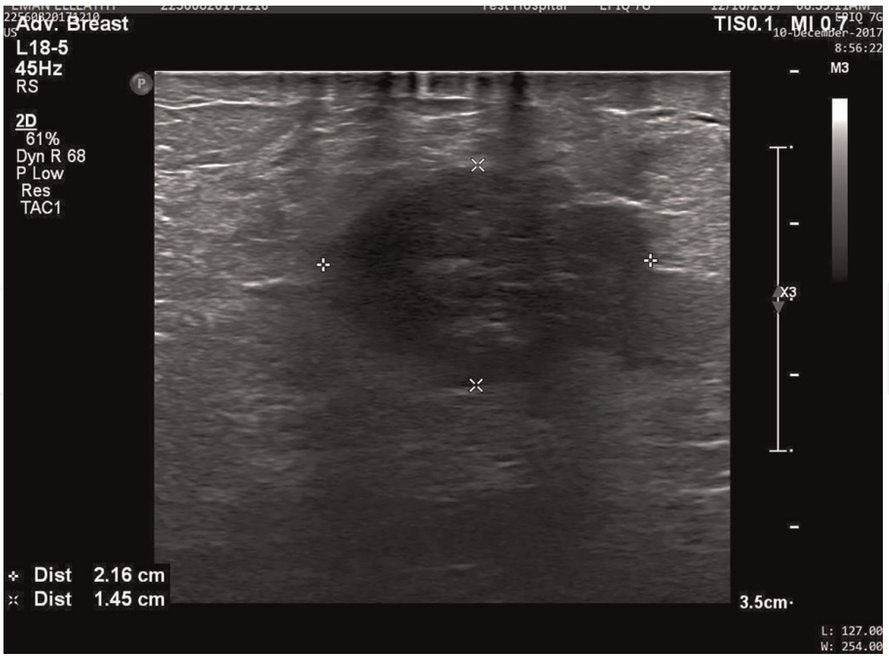

Figure 6.
U/S breast showing hypoechoic oval shaped lesion with circumscribed margin, measuring 2.2x1.5 cm in its maximum dimensions showing mixed posterior acoustic shadowing and enhancement. The lesion is not surrounded by desmoplastic reaction. No associated parenchymal distortion or calcification noted.

4.7 HER2 breast cancer case presentation

52-years-old female patient presented with right breast lump.
Family history: Positive (**Figure 7**).
Histopathological examination result:
Invasive ductal carcinoma grade III.

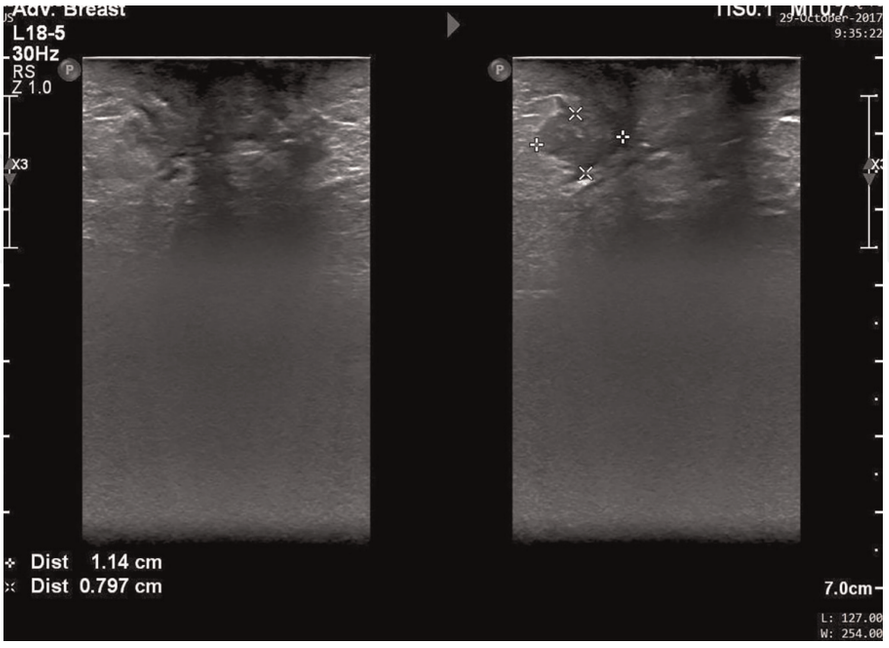

Figure 7.
U/S of breast showing hypoechoic irregular shaped lesion. The lesion was associated with parenchymal distortion and other satellite lesions. The largest measuring 1.2 x 2.1 cm in its maximum dimensions.

Immunohistochemistry revealed:
ER: negative
PR: negative
HER2: positive.

The current study comprised 40 female patients with breast cancer.
When analyzing the main four breast cancer subtypes. The present results showed the percentage rates of the subtypes-as: LA 34%. LB 40%, HER2 15%, and TNBC 11%.

The result of the present work showed LB subtype represented 40% and the cases followed by LA subtype 34%. While [6] in their study showed that LA subtype was 37.8°(.o and LB subtype was 36.8%.

The differences between the current work and [6] did not rank to valuable statistical difference.

The mean age of the patients was 50 +/− 10 with a range from 45 to 65:years. Correlation between each subtype.with age and density had been done. The significance of the correlation of subtype of the lesion and density of the breast was related to the age groups.

Since dense fibroglandular breast was associated with younger age group and fatty breast was associated with older age group was described by [7].

In the present study, LA subtype included 14 patients with 8 patients > 50 years and 6 patients <50 years. The result was not consistent with [8] study which had reported that most of LA patients' age was above 50 years.

LB subtype represented 16 patients of the current study with 10 patients> =50 years and 6 patients <50 years. The result was congruent with [8] which showed a higher percentage of the studied LB patients were less than 50 years of age.

HER2 subtype included 15 patients of our study with 6 patients>50 years and 9 patients<50 years. This was consistent with [6]. They found that HER2 breast cancer lesions were significantly associated with advanced age.

TNBC subtype included 4 patients, 3 of them were > 50 years and one patient < 50 years. Which indicates that TNBC was more associated with younger age group. The same results had been founded by [6, 9] studies that showed the majority of TNBC lesions were encountered with younger age group.

In the present study, HER2 lesions were more encountered in fatty breast. However the rest of subtypes showed no significant predominance in a certain: breast density. These findings were consistent with [8] findings that showed that HER2 subtype was significantly observed in postmenopausal women; but inconsistent in TNBC subtype. In the present work TNBC showed a strong association with dense fibroglandular breast.

Oval shaped lesions with circumscribed margin were found significantly associated with TNBC lesions (69% of the cases) ($p < 0.001$) and least observed in LA lesions where only 11% of them showed oval circumscribed margin. In contrast–irregular.-shaped lesions were significantly observed in LA subtype (88% of the cases) with a P value.

< 0.001. In addition 76% of LB cases and 73% of HER2 cases were associated with irregular shape ($P < 0.001$).

Speculated margin was observed in most of LA lesions (76% of the cases), while lobulated margin was more observed in HER2 lesions (66.7%).These findings were congruent with [9–11] findings. They showed tumors with regular shape and circumscribed margins were more often triple negative breast cancer lesions showing

hormone negativity while irregular shape and non-circumscribed margins was significantly associated with luminal tumors and hormone receptor positivity.

In the present study posterior shadowing was significantly associated with luminal tumors while posterior enhancement was found to be more observed with TNBC lesions (53%). Mixed enhancement and shadowing were associated with HER2 lesions which was observed in 53.3% of our HER2 cases.

These findings were consistent with [12] had stated that posterior enhancement is an eminent feature characterizing TNBC.

Kin et al. [13] findings were typically consistent with our study regarding the posterior acoustic shadowing feature in luminal subtypes. The current our results were not associated with [14] that showed that HER2 lesions were more associated with posterior enhancement.

Desmoplastic reaction was observed in LA lesions (55.5% of LA cases) with a P value < 0.001. Other subtypes showed no significant correlation with this criterion. Our finding was typically consistent with [6, 9] findings suggesting that desmoplastic reaction could denote slowly growing tumors.

All lesions were found to be more hypoechoic than isoechoic.

Hyperechoic lesions were not found at all in all the examined masses. Hypoechogenieity was significantly associated with TNBC, a result that found to be consistent with the one reported by [13].

Multiplicity of the lesion was more frequently encountered in HER2 subtype lesions and was not significantly observed in other subtype. This _is consistent with [13] that related this finding to the associated intraductal component that is found to be clearly associated with HER2+ receptor.

In the present study calcifications was found to be clearly encountered in ER2, subtyp lesions (,67%) with much less association with other subtype (P = 0.025).

This was found to be in accordance with [15] showing that the expression of HER2 oncogene was strongly correlated with the presence of calcification upon ultrasound. Additionally [12] noticed that the presence of calcification was significantly associated with HER2+ status.

Associated parenchymal distortion was more observed in LA and HER2 subtypes. This was consistent with [15] study that showed that LB subtype was the least associated with architectural distortion. Intraductal extension in HER2 subtype might have a role in architectural distortion as stated by [13].

Tumors larger than 2 cm were frequently associated with HER2+ status. These included HER2 and LB HER2+ subtypes which both together constitute 33% of total number of cases (P = 0.036). Smaller lesions were significantly seen in hormone receptor ER and /or PR positive breast masses. These results were correlated to the findings of [8].

TNBC lesions less than 2 cm were observed in one out of four patients, while the remaining three lesions were more than or equal 2 cm, and these findings were not consistent with [8, 16]. They showed that larger lesions were more associated with TNBC subtype. Invasive ductal carcinoma was the histopathological type the most common of breast cancer in the present study. Invasive lobular breast tumor was encountered in 23% of LA subtype's masses.

5. Conclusion

The sonographic features as margin shape, posterior acoustic features were significantly associated with molecular subtypes. The histopathological grade and hormone

receptor status. Being able to predict the molecular subtype. The current study recommend that the radiologist should•·b aware about different imaging features of different molecular subtypes especially the triple negative breast cancer which had the most benign looking criteria aiming for better lesion characterization and to allow the patient to benefit from earlier non invasive, cheap diagnosis and the curable on time management.

Author details

Eman Soliman Metwally, Rahma Mohammed Abed Alghazal* and Ah Haggaa Ali
Faculty of Medicine, Department of Radiology, Ain Shams University, Egypt

*Address all correspondence to: rahmaalghazal3@gmail.com

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