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Ultrasound and Mammographic Findings as Predictors of Biological Markers in Breast Cancer: Retrospective Analysis

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Abstract

Background: Breast cancer is a leading cause of death among women globally. Mammography and ultrasound, guided by the Breast Imaging Reporting and Data System (BI-RADS), are critical tools for distinguishing benign from malignant breast lesions. Advances in molecular subtyping, including luminal subtypes, HER2-enriched, and triple-negative breast cancer (TNBC), have revolutionized breast cancer management by enabling personalized treatment.

Aim of Study: The aim of this study is to use ultrasound and mammographic morphological features predictors of biological markers in patients with breast cancer.

Patients and Methods: This retrospective study involved 57 female patients with histopathologically confirmed malignant breast lesions. All patients underwent standard mammography and high-resolution ultrasound, followed by ultrasound-guided core biopsies. Immunohistochemical analysis determined hormone receptor status, including estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). The Allred scoring system evaluated ER/PR expression, and equivocal HER2 cases underwent fluorescence in situ hybridization (FISH) testing. Statistical analysis was conducted using RStudio, with $p<0.05$ deemed significant.

Results: Imaging features correlated significantly with molecular subtypes. Luminal subtypes showed irregular shapes, spiculated margins, hypoechoic echo patterns, and posterior shadowing ($p<0.001$). HER2-enriched lesions were associated with suspicious calcifications ($p=0.002$). TNBC presented with round shapes and circumscribed margins, mimicking benign lesions ($p<0.001$).

Conclusion: Molecular subtypes of malignant breast lesions can often be predicted by specific imaging features on mammography and ultrasound. However, histopathological confirmation remains essential. Radiologists must recognize that aggressive subtypes like TNBC may exhibit benign imaging appearances, emphasizing the need for integrating imaging and pathological findings for accurate diagnosis and optimal management.

Key Words: *Breast cancer – Mammography – Ultrasound – BI-RADS system – Molecular subtypes – HER2-enriched lesions – Triple-negative breast cancer – Imaging diagnostics – Digital mammography.*

Introduction

BREAST cancer is the leading cause of death among women around the world. Mammography and ultrasound are the main imaging diagnostic tools for the detection and diagnosis of breast cancer and are used in distinguishing between benign and malignant breast lesions **[1,2].** Diagnosis by ultrasound and mammogram depends mainly on the BI-RADS system assigned by the ACR which depends mainly on the morphological features (shape, margins, orientation, echo-pattern/density, calcifi-

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List of Abbreviations:

ACR : American College of Radiology.
BI-RADS : Breast Imaging Reporting and Data System.
CC : Craniocaudal.
ER : Estrogen Receptor.
FFDM : Full-Field Digital Mammography.
FISH : Fluorescence In Situ Hybridization.
HER2 : Human Epidermal Growth Factor Receptor 2.
IQR : Interquartile Range.
MLO : Mediolateral.
PR : Progesterone Receptor.
TNBC : Triple-Negative Breast Cancer.

cations, and associated features) in the description and differentiation between benign and malignant lesions [3,4].

Many studies nowadays focus on examining the molecular patterns of breast cancer in order to categorize these tumors into classes or entities contributing to clinical management, epidemiological and functional investigations, and clinical trials [5,6].

Four therapeutically important molecular subgroups have been identified based on extensive gene expression profile studies: Luminal subtypes (including Luminal A and B) HER2 enriched, and Triple Negative (TNBC) [7].

The genes associated with the expression of estrogen receptors (ER), progesterone receptors (PR), Human epidermal growth factor receptor 2 (HER2), and cell proliferation regulators are primarily responsible for the segregation of molecular subtypes of breast cancer [8].

Nowadays, the management of breast cancer depends mainly on molecular subtypes that can change the type of management in most patients by either using chemotherapy, radiotherapy, hormonal therapy, or going directly for surgical excision [7].

Patients and Methods

Patient selection:

This retrospective study was performed on 57 female patients histopathologically proven to have malignant breast lesions. The study was approved by the institution's ethics committee. An informed consent was obtained from all the examined patients before their inclusion in our study. This study was approved by the Research Ethics Committee of in 2022 (reference number 0107323, IRB number 00012098). Written informed consent was obtained from all patients included in this study. Inclusion criteria involved female patients within the fertile and post-menopausal age groups with malignant breast lesions candidates for mammography. Also, only patients suitable for true cut biopsy were included.

Exclusion criteria included patients with benign breast lesions, patients with malignant breast lesions diagnosed by FNAC only, or patients with unavailable histopathological data or whose paraffin blocks did not contain enough material for histopathological assessment of the grade and immunohistochemical staining for molecular subtyping.

Mammographic technique:

Standard craniocaudal (CC) and mediolateral Oblique (MLO) mammographic views were done for all examined patients using a dedicated full-field digital mammographic machine (FFDM) named (Hologic Selenia, Holland,2018) and (Mammomat Inspiration, Siemens, Germany, 2019) The images were viewed and interpreted by two experienced radiologists with 10 and 5 years of experience in breast imaging. Interpretation included breast imaging reporting and data system lexicon (ACR BI-RADS system) according to shape, margins, density, calcifications, and associated features [3].

Ultrasound technique:

All patients were examined using high resolution bilateral ultrasonographic examination using ultrasonographic equipment (GE LOGIC P5 machine) with 12 MHz linear transducer. The images were viewed and interpreted by two radiologists with more than 10 years of experience in sono-mammographic imaging, also applying breast imaging reporting and data system lexicon (ACR BI-RADS system) according to shape, margins, orientation, echo-pattern, and associated features.

Ultrasound-guided core biopsy:

Multiple complete core biopsies (at least 4-5 in number for each lesion) were obtained from different parts of the tumor of 1-2cm length of complete tissue using a 14-gauge needle and 16 to 18-gauge needle for small breast lesions and fixed using buffered formaldehyde then sent for histopathological assessment and immunohistochemical staining.

Pathological and immune-histochemical analysis:

For thirteen out of fifty-seven included patients, biopsies were referred to the pathology department at Alexandria Main University for histopathological examination. Formalin-fixed paraffin-embedded tissue blocks were prepared for the cases; from which 5-micron-thick slides were stained using hematoxylin and Eosin following the manufacturer's protocol. Four micron thick sections were prepared and stained using Ventana Benchmak Ultra Immuostainer for antiestrogen receptor (Clone Sp1), anti-progesterone receptor (clone 1E2), and antiHer2/neu (Clone 4B5) rabbit monoclonal primary antibodies. The slides were examined under light microscopy (Olympus CX23).

For the remaining 44 cases, pathological and immunohistochemical data were obtained and revised from patients' records and available slides.

The Allred scoring system was applied for ER and PR slides, which is based on the intensity of staining and the percentage of positive nuclei. ER and PR hormone receptors were considered positive when the Allred score was at least 3/8. Also, the grading system for HER 2 staining was applied and scored from 0 to 3+. Scores of 0 and 1+ were considered negative, Score 3+ was considered positive while Score 2+ was considered equivocal. Cases of 2+ scores were referred for reflex fluorescence in situ hybridization (FISH) testing for Her2 gene amplification.

Statistical analysis:

Data were collected, coded, revised, and entered into the Statistical Package for Social Science (RStudio) version 2.3.2. The data were presented as numbers and percentages for qualitative data; mean, standard deviations, and ranges for quantitative data with a parametric distribution; and median with interquartile range (IQR) for quantitative data with a non-parametric distribution. The Shapiro test was used to verify the normality of the distribution. Univariate and multivariate logistic regression analyses were performed to identify risk factors associated with a binary qualitative variable as a predictor and to calculate the odds ratio, measuring the strength of the relationship between risk factors and predictors. The confidence interval was set at 95%, and the accepted margin of error was set at 5%, with the p-value considered significant as follows: values greater than 0.05 were deemed non-significant (NS), values less than 0.05 were considered significant (S), and values less than 0.01 were considered highly significant (HS).

Results

In this study, fifty-seven female patients diagnosed with malignant breast lesions were included based on imaging characteristics and confirmed histopathological findings. The patients' ages ranged from 27 to 87 years, with a mean age of 55.7±14.5 years. The highest prevalence of cases was observed in the sixth decade (50–59 years).

Mammographic assessment was performed on only 52 patients (91.2%) who had mass lesions. Among these, 38 masses (73.1%) had an irregular shape, while 14 masses (26.9%) were regular. Spiculated margins were noted in 22 out of the 52 masses (42.3%), micro-lobulated margins in 11 cases (21.2%), indistinct margins in 4 cases (7.7%), and obscured margins in 2 cases (3.8%). Circumscribed margins were observed in 13 cases (25%). Additionally, all mass lesions (100%) demonstrated high density.

Associated findings included asymmetry in 48 of the 52 patients with mass lesions (92.3%), while no associated asymmetry was observed in 4 patients (7.7%). Parenchymal architectural distortion was present in 25 of the cases with mass lesions (48.1%), whereas 27 patients (51.9%) showed no parenchymal distortion. (Table 1).

Suspicious calcifications were identified in 21 out of 57 patients (36.8%), with various morphological patterns, including fine pleomorphic, coarse heterogeneous, fine linear branching, and amorphous types. In contrast, 36 patients (63.2%) showed no calcifications. Skin thickening was observed in 38 patients (66.7%), while nipple retraction was noted in 3 patients (5.3%), and skin retraction in 2 patients (3.5%). Axillary adenopathy was present in 53 of the 57 patients (93%). (Table 2).

Sonographic evaluation revealed mass lesions in 52 patients (91.2%). Of these, 38 masses (73.1%) were irregular in shape, while 14 (26.9%) were regular. Marginal characteristics included spiculated margins in 22 of the masses (42.3%), micro-lobulated margins in 9 (17.3%) and angulated margins in 8 (15.4%). Circumscribed margins were observed in 13 cases (25%).

Large lesions (>2cm) were identified in 39 out of 52 patients (75%), while smaller lesions (<2cm) were observed in 13 patients (25%). Lesion location varied, with 40 out of 52 masses (76.9%) situated superficially (within 1cm of the skin surface) and 12 (23.1%) located deeper (>1cm from the skin surface). Hypoechoic mass lesions were present in 46 patients (88.5%), and 6 patients (11.5%) showed masses with mixed solid and cystic components.

Approximately 34 of 52 patients (65.4%) exhibited a nonparallel orientation of the mass relative to the skin surface, while 18 patients (34.6%) showed a parallel orientation. Posterior shadowing was observed in 34 patients (65.4%), and posterior enhancement was noted in 10 patients (19.2%). Combined posterior features were present in 1 patient (1.9%), while 7 patients (13.5%) had no associated posterior features. Parenchymal architectural distortion was identified in 25 with mass lesions (48.1%) (Table 3).

Regarding molecular subtypes, 37 patients (64.9%) had luminal breast cancer, 7 patients (12.3%) had HER2-enriched breast cancer, and 13 patients (22.8%) had triple-negative breast cancer (TNBC). Tables (4,5), as well as Tables (6,7), display the distribution of mammographic and sonographic features across different molecular subtypes of breast lesions (HER2-enriched, luminal subtypes, and TNBC) and highlight the statistical significance of each feature in predicting specific molecular subtypes.

Sono-mammographic malignant features, such as irregular shape, spiculated margins, nonparallel orientation, hypoechoic echo pattern, and associated posterior shadowing, were predominantly observed in lesions of the luminal subtype. These characteristics were found in 34 patients (59.6%) with a *p*-value of <0.001 (Fig. 1). HER2-enriched lesions were more commonly associated with suspicious calcifications, with a p-value of 0.002 (Fig. 2). Conversely, features suggestive of benign morphology, such as rounded shape and circumscribed margins, were more frequent in TNBC lesions, with a *p*-value of <0.001 (Figs. 3,4).

Table (1): The Distribution of all studied patients according to morphological mammographic features applying BI-RADS lexicon year 2015 in patients with mass lesions (n=52).

Mass (n=52)	
Shape:	
- Oval	2 (3.8%)
- Rounded	12 (23.1%)
- Irregular	38 (73.1%)
Margin:	
- Circumscribed	13 (25.0%)
- Obscured	2 (3.8%)
- Micro-lobulated	11 (21.2%)
- Indistinct	4 (7.7%)
- Spiculated	22 (42.3%)
Density:	
- Low	–
- High	52 (100.0%)
- Iso	–
Associated Asymmetry:	
- No	4 (7.7%)
- Asymmetry	–
- Focal	42 (80.8%)
- Global	6 (11.5%)
- Developing	–
Associated Architectural distortion:	
- No	27 (51.9%)
- Yes	25 (48.1%)

Table (2): The Distribution of all studied patients according to morphological mammographic features applying BI-RADS lexicon year 2015 (n= 57).

Calcifications (n=57)	
No	36 (63.2)
Typically benign:	
Suspicious:	
- Amorphous	1 (4.8%)
- Coarse heterogeneous	4 (19%)
- Fine pleomorphic	15 (71.4%)
- Fine linear/fine linear branching	1 (4.8%)
Associated features:	
- Skin thickening	38 (66.7%)
- Skin retraction	2 (3.5%)
- Nipple retraction	3 (5.3%)
- Axillary adenopathy	53 (93.0%)

Table (3): The Distribution of all studied patients according to morphological sonographic features applying BI-RADS lexicon year 2015 in patients with mass lesions (n=52).

Mass lesions (n=52)	
Shape:	
- Oval	2 (3.8%)
- Rounded	12 (23.1%)
- Irregular	38 (73.1%)
Margin:	
- Circumscribed	13 (25.0%)
Non-circumscribed:	
- Micro-lobulated	9 (17.3%)
- Angulated	8 (15.4%)
- Spiculated	22 (42.3%)
Size:	
- Small (≤2cm)	13 (25.0%)
- Large (>2cm)	39 (75.0%)
Depth:	
- Superficial (≤1cm from skin)	40 (76.9%)
- Deep (>1cm from skin)	12 (23.1%)
Echogenicity:	
- Hypoechoic	46 (88.5%)
- Isoechoic	-
- Hyperechoic	-
- Anechoic	-
- Mixed solid and cystic	6 (11.5%)
Orientation:	
- Parallel	18 (34.6%)
- Not parallel	34 (65.4%)
Posterior features:	
- No	7 (13.5%)
- Enhancement	10 (19.2%)
- Shadowing	34 (65.4%)
- Combined	1 (1.9%)
Associated Architectural distortion:	
- No	27 (51.9%)
- Yes	25 (48.1%)

Table (4): The correlation between molecular subtypes and mammographic morphological features of mass lesions (n=52).

Mass (n=52)	HER 2 enriched (n=4)	Luminal subtypes (n=35)	TNBC (n=13)	*p*-value
Shape (mammogram):				
- Oval	0 (0.0%)	0 (0.0%)	3 (23.1%)	$\chi2$=42.618*
- Rounded	0 (0.0%)	1 (2.85%)	10 (76.9%)	(^{MC}p<0.001*)
- Irregular	4 (100.0%)	34 (97.1%)	0 (0.0%)	
Margin:				
- Circumscribed	0 (0.0%)	1 (2.8%)	12 (92.3%)	$\chi2$=41.054
- Obscured	0 (0.0%)	2 (5.7%)	0 (0.0%)	(^{MC}p<0.001*)
- Micro-lobulated	0 (0.0%)	10 (28.5%)	1 (7.7%)	
- Indistinct	0 (0.0%)	4 (11.4%)	0 (0.0%)	
- Spiculated	4 (100.0%)	18 (51.4%)	0 (0.0%)	
Density:				
- Low	0 (0.0%)	0 (0.0%)	0 (0.0%)	–
- High	4 (100.0%)	35 (100.0%)	13 (100.0%)	
- Iso	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Associated asymmetry:				
- No	0 (0.0%)	4 (11.4%)	0 (0.0%)	$\chi2$=3.799
- Asymmetry	0 (0.0%)	0 (0.0%)	0 (0.0%)	(^{MC}p=0.746)
- Focal	3 (75.0%)	27 (77.1%)	12 (92.3%)	
- Global	1 (25.0%)	4 (11.4%)	1 (7.7%)	
- Developing	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Associated architectural distortion:				
- No	0 (0.0%)	18 (51.4%)	9 (69.2%)	$\chi2$=6.877
- Yes	4 (100.0%)	17 (48.5%)	4 (30.8%)	(^{MC}p=0.074)

Table (5): The correlation between molecular subtypes and mammographic calcifications and associated features (n=57).

Calcifications (n=57)	HER 2 enriched (n=7)	Luminal subtypes (n=37)	TNBC (n=13)	*p*-value
At mammogram:				
No	0 (0.0%)	24 (64.8%)	12 (92.3%)	$\chi2$=16.734* (^{MC}p=0.001*)
Typically benign:				
Suspicious:	7 (100.0%)	13 (35.1%)	1 (7.7%)	
- Amorphous	1 (14.3%)	0 (0.0%)	0 (0.0%)	$\chi2$=3.324 (^{FE}p=1.000)
- Coarse heterogeneous	1 (14.3%)	3 (23%)	0 (0.0%)	$\chi2$=1.286 (^{MC}p=1.000)
- Fine pleomorphic	5 (71.4%)	9 (69.23%)	1 (100.0%)	$\chi2$=0.824 (^{MC}p=1.000)
- Fine linear/ fine linear branching	0 (0.0%)	1 (7.6%)	0 (0.0%)	$\chi2$=3.633 (^{MC}p=0.340)
Associated features:				
- Skin thickening	5 (71.4%)	24 (64.8%)	8 (61.5%)	$\chi2$=0.479 (^{MC}p=0.959)
- Skin retraction	1 (14.3%)	1 (2.7%)	0 (0.0%)	$\chi2$=3.128 (^{MC}p=0.358)
- Nipple retraction	0 (0.0%)	3 (8.1%)	0 (0.0%)	$\chi2$=1.526 (^{MC}p=0.852)
- Axillary adenopathy	5 (71.4%)	36 (97.2%)	11 (84.6%)	$\chi2$=5.381 (^{MC}p=0.080)

Table (6): The correlation between molecular subtypes and sonographic morphological features of mass lesions (n=52).

Mass (n=52)	HER 2 enriched (n=4)	Luminal subtypes (n=35)	TNBC (n=13)	*p*-value
Shape:				
- Oval	0 (0.0%)	0 (0.0%)	3 (23.1%)	$\chi2$=42.618*
- Rounded	0 (0.0%)	1 (2.8%)	10 (76.9%)	(*p*<0.001*)
- Irregular	4 (100.0%)	34 (97.1%)	0 (0.0%)	
Margin:				
- Circumscribed	0 (0.0%)	1 (2.8%)	12 (92.3%)	$\chi2$=41.348* (*p*<0.001*)
Non-circumscribed:				
- Micro-lobulated	0 (0.0%)	8 (22.8%)	1 (7.7%)	
- Angulated	0 (0.0%)	8 (22.8%)	0 (0.0%)	
- Spiculated	4 (100.0%)	18 (51.4%)	0 (0.0%)	
Size:				
- Small (≤2cm)	1 (25%)	11 (31.4%)	1 (7.7%)	$\chi2$=6.885
- Large (>2cm)	3 (75%)	24 (68.57%)	12 (92.3%)	(*p*=0.068)
Echogenicity:				
- Hypoechoic	4 (100.0%)	35 (100.0%)	7 (53.8%)	$\chi2$=14.391*
- Isoechoic	0 (0.0%)	0 (0.0%)	0 (0.0%)	(*p*<0.001*)
- Hyperechoic	0 (0.0%)	0 (0.0%)	0 (0.0%)	
- Anechoic	0 (0.0%)	0 (0.0%)	0 (0.0%)	
- Mixed solid and cystic	0 (0.0%)	0 (0.0%)	6 (46.2%)	
Orientation:				
- Parallel	0 (0.0%)	7 (20.0%)	11(84.6%)	$\chi2$=18.084*
- Not-parallel	4 (100.0%)	28 (80.0%)	2 (15.4%)	(*p*<0.001*)
Posterior features:				
- No	1 (25.0%)	2 (5.7%)	4 (30.8%)	$\chi2$=38.302*
- Enhancement	0 (0.0%)	1 (2.8%)	9 (69.2%)	(*p*<0.001*)
- Shadowing	3 (75.0%)	32 (91.4%)	0 (0.0%)	
- Combined	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Associated architectural distortion:				
- No	0 (0.0%)	18 (51.4%)	9 (69.2%)	$\chi2$=6.877
- Yes	4 (100.0%)	17 (48.57%)	4 (30.8%)	(*p*=0.076)

Table (7): The correlation between molecular subtypes and sonographic calcifications and associated features (n=57).

Calcifications (n=57)	HER 2 enriched (n=7)	Luminal subtypes (n=37)	TNBC (n=13)	*p*-value
At ultrasound:				
- No	0 (0.0%)	26 (70.2%)	11(84.6%)	$\chi2$=17.937*
- In mass	4 (57.1%)	10 (27.02%)	2 (15.4%)	(*p*=0.002*)
- Outside mass	3 (42.9%)	1 (2.7%)	0 (0.0%)	
Associated features: - Skin thickening	5 (71.4%)	24 (64.8%)	8 (61.5%)	$\chi2$=0.479 (*p*=0.956)
- Skin retraction	1 (14.3%)	1 (2.7%)	0 (0.0%)	$\chi2$=3.128 (*p*=0.359)
- Nipple retraction	0 (0.0%)	3 (8.1%)	0 (0.0%)	$\chi2$=1.526 (*p*=0.851)
- Axillary adenopathy	5 (71.4%)	36 (97.2%)	11(84.6%)	$\chi2$=5.381 (*p*=0.079)
- Internal vascularity	4 (57.1%)	35 (94.5%)	7 (53.8%)	$\chi2$=12.022* (0.003*)
- Rim vascularity	0 (0.0%)	0 (0.0%)	6 (46.2%)	$\chi2$=15.208* (*p*<0.001*)

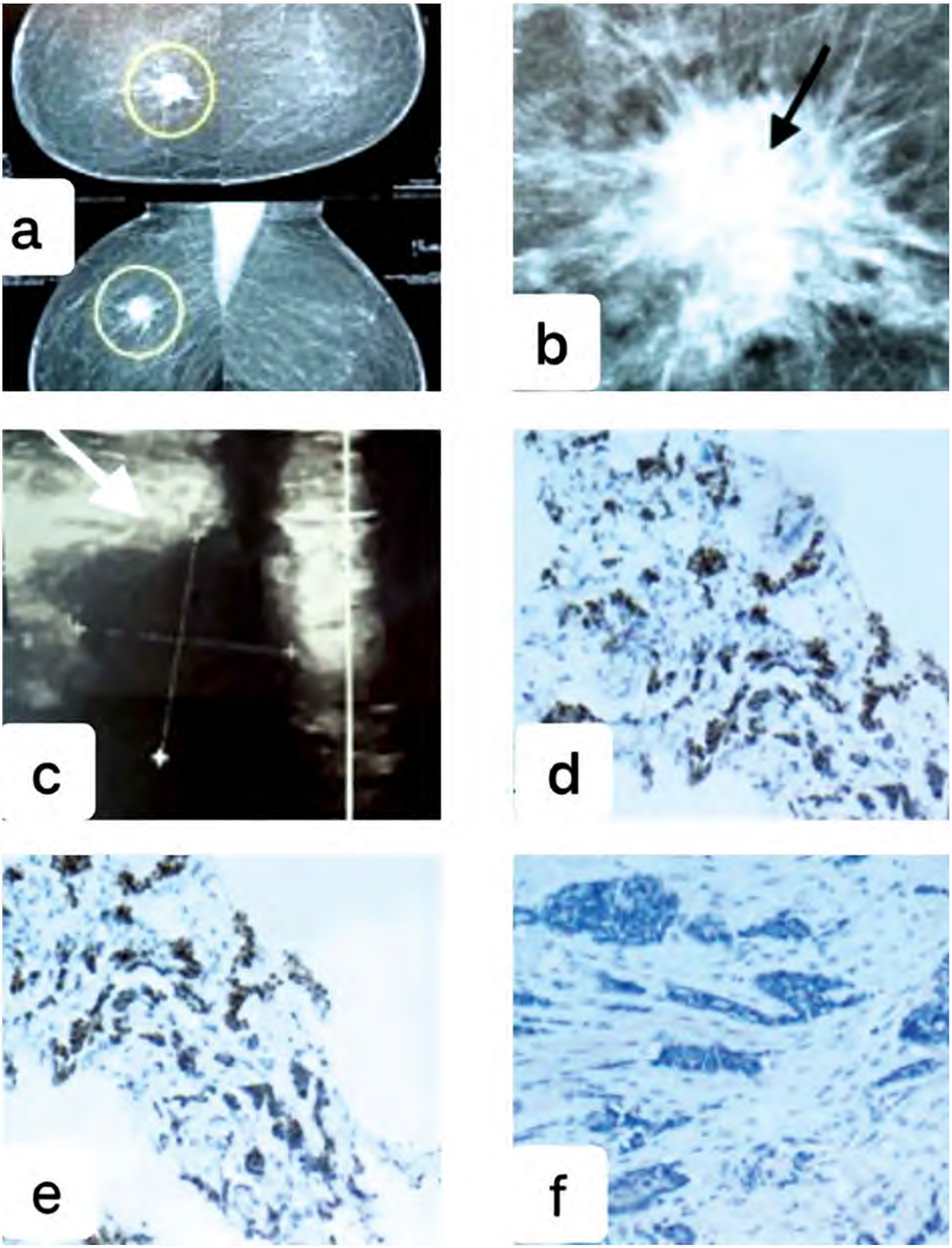

Fig. (1): (Luminal subtypes) (A) CC and MLO mammographic views revealed irregular shaped lesion with spiculated margins and (B) Fine pleomorphic calcifications. (C) B mode US showed irregular shape, angulated margins and nonparallel orientation. Pathology: grade 3. Biological markers: (D) ER positive (ER IHC stain), (E) PR positive (PR IHC stain) and (F) HER-2 negative (score 1+) (HER2 IHC stain).

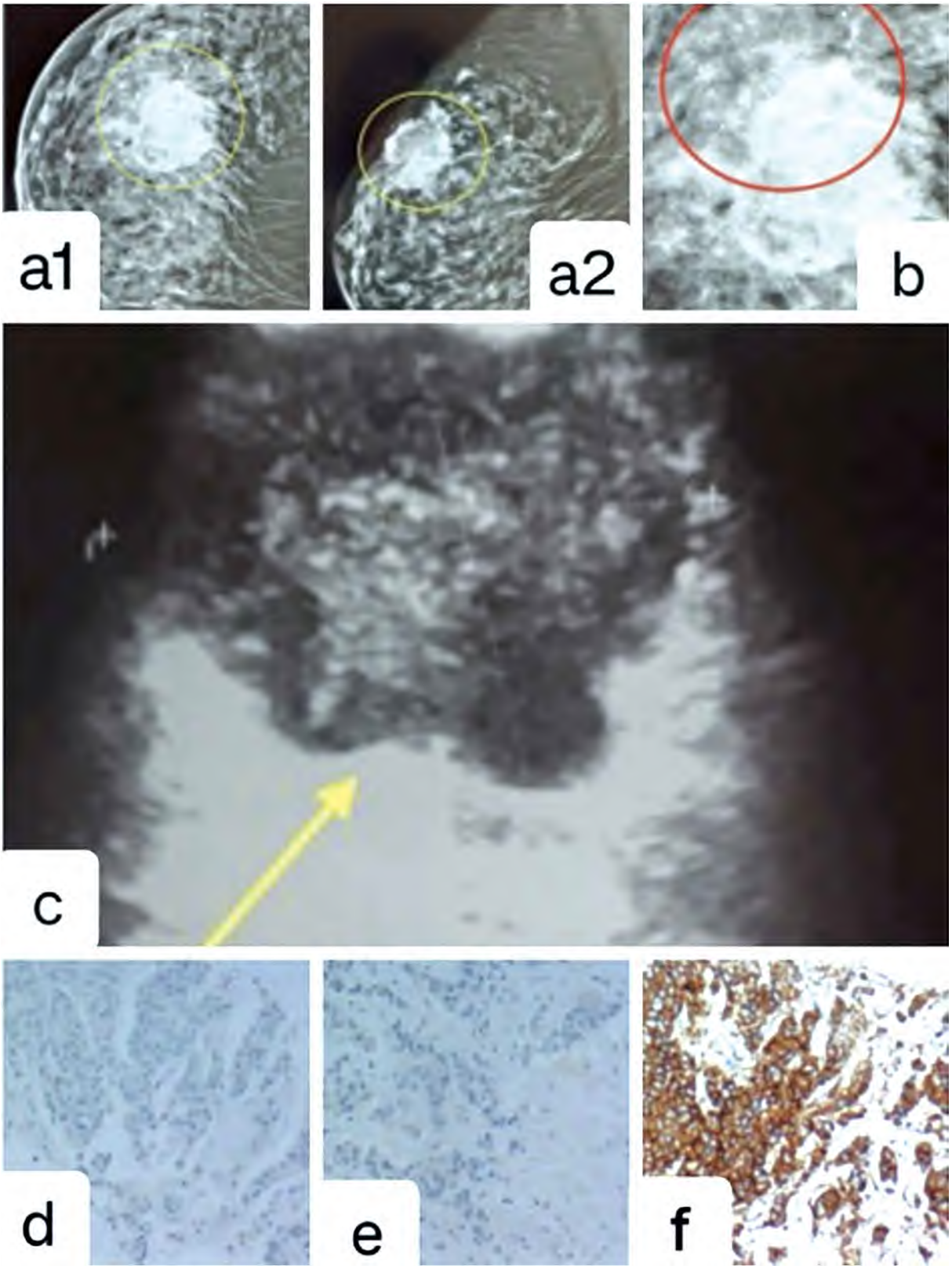

Fig. (2): (HER2 enriched subtype) (A1-A2) CC and MLO mammographic views revealed irregular shaped lesion with macro-lobulated margins and (B) fine pleomorphic calcifications. (C) B mode US showed irregular shape, microlobulated margins and non-parallel orientation associated with suspicious calcifications in mass. Pathology: (Grade 2). Biological markers: ER negative (ER IHC stain), PR negative (PR IHC stain) and HER-2 positive (score 3+) (HER2 IHC stain).

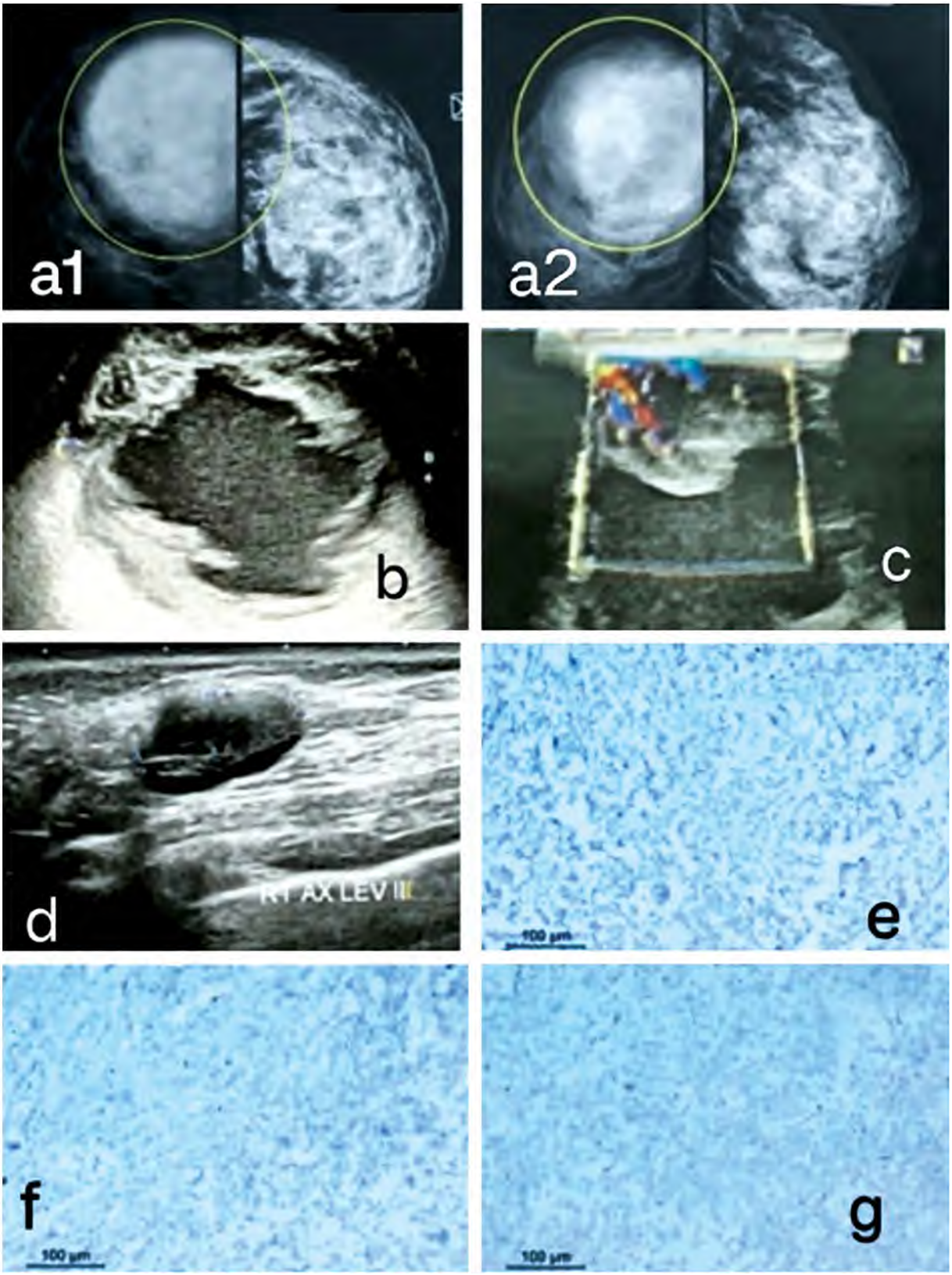

Fig. (3): (TNBC subtype) (A1-A2) CC and MLO mammographic views revealed rounded shaped lesion with circumscribed margins and no detected suspicious calcifications. (B,C,D) B mode US showed oval shape, circumscribed margins and parallel orientation associated with posterior enhancement (b) and peripheral vascularity on color doppler (C) as well as suspicious axillary LN (D). Pathology: Grade 3. Biological markers: ER negative ER IHC stain), PR negative (PR IHC stain) and HER-2 negative (score 1+) (HER2 IHC stain).

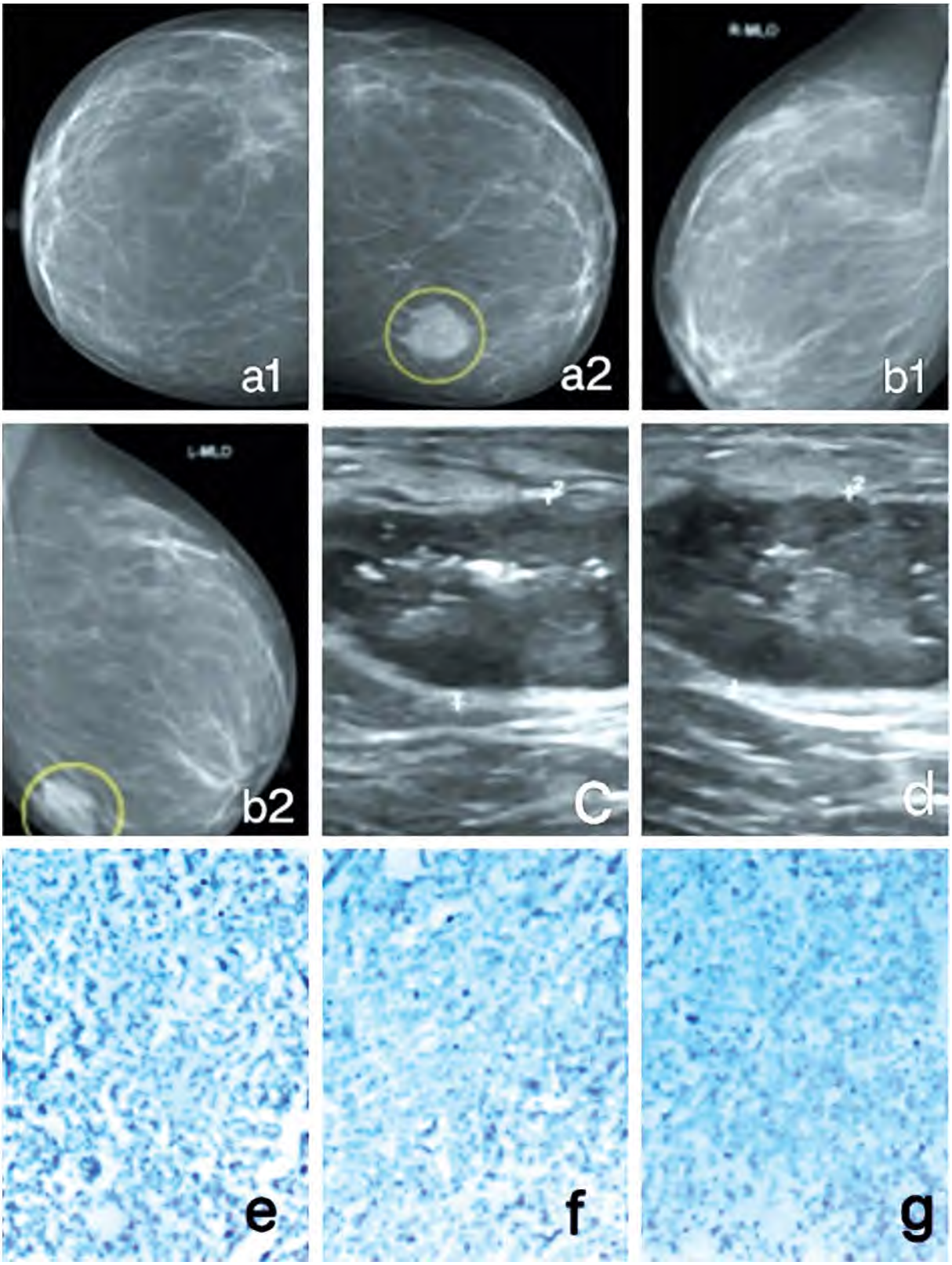

Fig. (4): (TNBC subtype) 32 years old female patient presented with left breast mass Mammographic findings: (A,B) Showing left breast lower inner quadrant high dense rounded lesion (yellow circle) with circumscribed margins with no detected suspicious calcifications Ultrasound findings: (C,D) Revealed a hypoechoic mass lesion at the site of clinically palpable mass showing oval shape with circumscribed margins and parallel orientation to the skin surface associated with posterior enhancement and internal vascularity on color doppler with suspicious axillary lymph nodes and few in-mass suspicious calcifications (C). Pathology: microscopic images (E) ER negative (ER IHC stain), (F) PR negative (PR IHC stain), (G) Show HER2 negative (score 1+) (HER2 IHC stain).

Discussion

Early diagnosis of breast cancer is the major role of breast sono-mammography, in addition to differentiation between benign and malignant lesions which significantly impacts upon the early diagnosis and management of breast cancer. Diagnosis by ultrasound and mammogram relies mainly on the BI-RADS system assigned by the ACR which depends mainly on the morphological features in the description and differentiation between benign and malignant lesions *[9,10]*.

This study was done in an attempt to correlatethe ultrasound and mammographic morphological features with pathological and biological markers in patients with malignant breast lesions for early prediction of tumor molecular subtype and early management. Recently the morphological features of breast lesions have been reported as being used to predict molecular subtypes which proved to have prognostic and therapeutic value in breast cancer patients *[11]*.

Thirty-seven patients were identified in our study with luminal subtypes, the majority of whom presented with mass lesions. Of the thirty-five patients with luminal subtypes and mass lesions, thirty-four had irregularly shaped lesions, while the remaining patient had a rounded lesion. In terms of margins, thirty-four patients exhibited non-circumscribed margins: Eighteen had spiculated margins, and sixteen had angulated or micro-lobulated margins. Only one patient had a circumscribed margin, with a statistically significant *p*-value of <0.001. These results can be used as predictors of luminal subtypes in agreement with those reported in the study of Ian TWM et al., who reported a predominance of irregular shape and non-circumscribed margins is luminal subtypes A and B lesions *[12]*. Non-parallel orientation was observed in 28 patients, with a significant *p*-value of <0.001, consistent with the observations of Elsaeid et al. that luminal A and B subtypes commonly display this characteristic *[11]*. Furthermore, posterior shadowing was detected in 32 mass lesions, while only one patient showed posterior enhancement, leading to a *p*-value of <0.001. This finding aligns with Jihyum Kim et al., who highlighted posterior shadowing as a notable feature of luminal subtypes *[13]*. Collectively, these results underscore the importance of imaging features in identifying and characterizing luminal breast cancer subtypes.

Interestingly, micro-calcifications were not associated with luminal subtypes in our study, which corroborates Ian TWM et al.'s findings that these calcifications are more common in HER2-enriched subtypes. Of the patients in our study, only 13 exhibited suspicious calcifications on mammograms, and 11 showed them on ultrasound, with 10 of these being mass lesions. However, these results were statistically insignificant.

On ultrasound, internal vascularity was observed in 35 patients with Luminal subtype mass lesions, which was statistically significant and consistent with previous findings by Ian TWM et al. *[12]*.

The analysis of HER2-enriched subtypes, 7 out of 57 patients were identified, with mass lesions detected in 4. The remaining patients presented with focal and global asymmetry and architectural distortion, confirming that non-mass lesions are more prevalent in HER2-enriched cases. This finding aligns with M. Boisserie et al., *[14]* who noted that non-mass lesions and intra-ductal extensions are common in HER2-enriched subtypes.

Furthermore, all four patients with HER2-enriched mass lesions displayed malignant morphological features, including irregular shapes and spiculated margins, yielding statistically significant results (*p*-value <0.001) *[14]*.

All patients with HER2-enriched subtypes exhibited hyperdense masses on mammograms, accompanied by focal and global asymmetry. The mass lesions also demonstrated a hypoechoic echo pattern on ultrasound, which was statistically significant (*p*-value <0.001). This is consistent with findings by Jihyum Kim et al., *[13]* indicating that hypoechoic lesions are more frequently associated with luminal and HER2-enriched subtypes compared to TNBC.

Our study also found that non-parallel orientation of the lesions was present in all examined patients, with this feature being statistically significant (*p*-value <0.001) specifically in the 4 patients with HER2-enriched lesions. This observation is consistent with the findings of Elsaeid et al., *[11]* who reported that non-parallel orientation is commonly observed in cases of the HER2-enriched subtype.

Posterior shadowing was observed on ultrasound examination in 75% of patients with HER2-enriched masses, while the remaining 25% exhibited no posterior sound effects. These results contrast with the findings of Kim et al., *[15]* who reported that posterior enhancement features are more commonly associated with the HER2-enriched subtype.

Moreover, all seven patients with mass and non-mass HER2-enriched lesions showed suspicious calcifications on both mammograms and ultrasounds, yielding statistically significant findings (*p*-value 0.002). These observations support Ian TWM et al.'s conclusion that suspicious calcifications are highly prevalent in HER2-enriched subtypes *[12]*.

In examining TNBC subtype, we identified 13 patients, all presenting as mass lesions. Previous studies by Schopp JG et al. *[16]* and Elsaeid et al., *[11]* indicated that regularly shaped lesions with

circumscribed margins are highly predictive of the TNBC subtype. Our findings support this, as all TNBC lesions exhibited regular shapes, including three oval and ten rounded lesions. Of these, 12 had circumscribed margins, while one displayed micro-lobulated margins, with a statistically significant *p*-value of <0.001.

All TNBC patients exhibited hyperdense masses on mammograms, which were associated with either focal or global asymmetry. On ultrasound, 7 out of 13 patients had hypoechoic masses, and 6 presented with mixed solid and cystic echo patterns, yielding statistically significant results (*p*-value <0.001). This is consistent with the findings of Schopp JG et al., *[16]* Kim et al., *[15]* and M. Boisserie et al., *[14]* who noted that the TNBC subtype often presents masses with central necrotic changes and mixed solid and cystic patterns.

Moreover, 12 patients with triple-negative lesions were identified as having large tumors (greater than 2cm), while only one mass was classified as small (less than 2cm) on ultrasound. These findings align with the study conducted by Ian TWM et al., *[12]* which demonstrated that if a lesion is large (greater than 2cm), the likelihood of it being a TNBC subtype increases by 13 times compared to non-TNBC types.

In our study, ultrasound findings indicated that 11 patients with TNBC had lesions exhibiting parallel orientation, while only two patients displayed non-parallel orientation, yielding statistically significant results (*p*-value <0.001), consistent with the findings of Elsaeid et al. *[11]*. Furthermore, Schopp JG et al., *[16]* noted that TNBC cases are often associated with posterior enhancement, likely due to cystic components. Our results supported this observation, as ultrasound examinations revealed that 9 out of 13 patients exhibited posterior enhancement, while 4 out of 13 had no significant posterior features, with statistically significant findings (*p*-value <0.001).

Additionally, all TNBC lesions in the current study demonstrated vascularity on ultrasound, with 7 out of 13 showing internal vascularity and 6 out of 13 exhibiting rim vascularity. These findings were also statistically significant (*p*-value <0.001) and corroborated the previous work by Schopp JG et al., which highlighted that peripheral vascularity is more prominent in TNBC patients, aiding in the differentiation between TNBC and benign lesions *[16]*.

This study's limitations include a relatively small sample size, which may impact the generalizability of the findings, and a retrospective design that could introduce selection bias, affecting subtype prevalence and correlations with imaging features. While our sample size was comparable to that of Elsaeid et al. *[11]* (65 female patients), these limitations emphasize the necessity for further research with larger cohorts to accurately determine the statistical significance of the observed morphological features.

Our findings indicate that Luminal subtypes (including luminal A and B) exhibit more malignant characteristics, such as irregular shapes, spiculated margins, hypoechoic echo patterns, and posterior shadowing, along with suspicious calcifications. These lesions often display internal vascularity on color Doppler imaging. In contrast, HER2-enriched luminal lesions are characterized by suspicious calcifications and show malignant features on sono-mammographic images. Most TNBC lesions were found to have circumscribed oval or rounded shapes with mixed solid and cystic components; these lesions tend to be larger and are associated with posterior enhancement and rim vascularity on color Doppler.

Conclusion:

Molecular subtypes have become an invaluable tool in determining the most suitable treatment protocols for breast cancer patients, offering critical insights that guide therapeutic decisions. In addition, morphological characteristics observed through ultrasound and mammography play a significant role in identifying specific tumor luminal subtypes. These imaging features contribute essential information for classifying the tumor's biology, and allowing for more precise predictions about patient outcomes.

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الموجات الصوتية والماموجرام فى التنبؤ بدرجة الورم والدلالات الحيوية فى أورام الثدى السرطانية

يُعدّ سرطان الثدى من أبرز الأسباب المؤدية للوفاة بين النساء حول العالم، ويمثل تحديًا صحيًا عالميًا. مع تطور التصنيف الجزيئى لأنواع سرطان الثدى مثل الأنواع اللمعية، والنوع الغنى، وسرطان الثدى الثلاثى السلبى أصبح من الممكن تكييف العلاج بشكل فردى وفقًا لخصائص الورم البيولوجية.

تهدف هذه الدراسة الاستعادية إلى استكشاف ما إذا كانت ملامح التصوير بالأشعة (الماموجرام والموجات فوق الصوتية) قادرة على التنبؤ بالأنماط الجزيئية للأورام السرطانية.

شملت الدراسة ٥٧ امرأة لديهن أورام خبيثة مؤكدة عن طريق التحليل النسيجى. خضع جميع المشاركات لتصوير الماموجرام الرقمى والموجات فوق الصوتية عالية الدقة، تلاه أخذ خزعات موجهة بالموجات فوق الصوتية. تم تقييم الحالة الهرمونية للورم (ER و PR وHER٢) باستخدام التحليل الكيميائى المناعى، وتم تأكيد الحالات غير الحاسمة لـHER٢ باختبار FISH.

أظهرت النتائج ارتباطًا واضحًا بين خصائص التصوير وأنواع السرطان الجزيئية. ظهرت الأنواع اللمعية بأشكال غير منتظمة، وحواف مشوكة، ونسيج ناقص الصدى، وظلال خلفية. أما الأورام الغنية بـHER٢ فقد تميزت بتكلسات مريبة فى التصوير الشعاعى. فى المقابل، أظهرت سرطانات الثدى الثلاثى السلبى صفات تشبه الأورام الحميدة، مثل الشكل المستدير والحدود الواضحة، مما قد يؤدي إلى سوء التقدير التشخيصى وخطر التأخير فى العلاج.

خلصت الدراسة إلى أن التصوير الإشعاعي يوفر مؤشرات مفيدة على طبيعة الورم، لكنه لا يغنى عن التأكيد النسيجى. من الضرورى أن يكون مختصو الأشعة على دراية بأن بعض الأنماط العدوانية، كالثلاثى السلبى، قد تظهر بمظاهر حميدة، مما يستدعى دمج نتائج التصوير مع التحاليل النسيجية للوصول إلى تشخيص دقيق وخطة علاجية مناسبة.