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Negative estrogen-receptor invasive breast carcinoma: mammographic aspects, correlations with HER2/neu oncoprotein status

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Abstract

This study involved 40 ER-negative female patients with invasive breast cancer, aged between 25 and 88 years, diagnosed at Emergency County Hospital of Craiova, Romania, during a two-year interval (2010–2011). All patients that took part in the study were subjected to a preoperative mammography exam, and later to HP and IHC exams, in order to detect the ER, PR and HER2 status. These exams were followed by CISH in ambiguous HER2 cases. The tumor detection method was palpation in 16 cases, whereas in 24 cases the method used was the screening mammography. Histopathologically, the analyzed tumors were infiltrative ductal carcinoma (35 cases), lobular carcinoma (one case), mucinous (two cases) and metaplastic carcinoma (two cases). Depending on the status of the oncoprotein HER2, the 40 ER-negative female patients included in the study formed two groups: the ER-negative, HER2-positive (11 cases, 27.5%) formed the first group and the ER-negative, HER2-negative (29 cases, 72.5%) formed the second group. Depending on the expression of the receptors for progesterone, 60% of cases were classified as triple negative mammary carcinomas (ER-, PR-, HER2-). The comparative study of the ER-negative, HER2-positive and the ER-negative, HER2-negative mammary carcinomas showed that the tumors of the ER-negative, HER2-positive group were mostly high degree cancers (80% *vs.* 56%), with negative progesterone receptors (81.81% *vs.* 48.27%), associated with axillary lymph node metastasis (63.63% *vs.* 48.27%), and were detected at a higher cancer stage (II/III) (81.81% *vs.* 62.06%). Regarding the mammographic features, the ER-negative HER2-positive breast cancers are more likely to be irregular masses (62.5% *vs.* 33.33%), with spiculated margins (45.45% *vs.* 6.9%), frequently associated with dense or heterogeneously dense breast (82% *vs.* 69%) and pleomorphic calcifications (62.5% *vs.* 28.57%) comparative with ER-negative HER2-negative cancers that were more frequently round/oval mass, with indistinct margins and a great variety of morphological types of calcifications. The correlations between imaging and clinical aspects, together with the biomarker expression in breast cancers may sooner suggest the biological characteristics of these tumors, thus hinting at their evolution and helping to identify female patients with invasive breast cancer that will positively respond to an aimed therapy.

Keywords: invasive breast cancer, hormone receptors, HER2 oncoprotein, mammography.

Introduction

Breast cancer is the most common malignancy of females all over the world and the second leading cause of death due to malignancy among females. The prognosis and management of breast cancer is influenced by classic variables as the histological type, grade and clinical stage, status of estrogen receptor (ER), progesterone receptor (PR) and more recently, HER2/neu status [1].

Breast cancer is a heterogeneous disease. Some breast cancer cells lose their ability to express ERα, among other proteins. The resulting disease is a therapy-resistant cancer [2] with a distinct history and prognostic profile [3, 4]. The ER-negative breast cancers account for 25–30% of all breast cancers, most of the patients with ER-negative tumors do not benefit from anti-hormonal therapy and many of these tumors are unaffected by conventional cytotoxic chemotherapeutic regimens [5, 6].

Approximately 25% of patients with breast cancer overexpress the human epidermal growth factor receptor type 2 or HER2, a membrane receptor protein encoded by a proto-oncogene(HER2/neu gene), located on the chromosome 17 (17q21). Amplification of the HER2/neu gene results in overexpression of HER2 protein [7].

Breast cancers, which represent the expression of HER2 protein and/or the amplification of HER2/neu gene, are considered HER2-positive cancers. Regarding the status of HER2, ER-negative breast cancers can be separated in two distinct subgroups: ER-negative HER2-negative breast cancers and ER-negative HER2-positive breast cancers with different biological characteristics [8].

Mammography is generally the first breast imaging procedure used in breast cancer screening or in the

assessment of women who present with breast signs or symptoms that may be indicative of cancer. The results of a mammogram need to be communicated to the referring physician in a consistent understandable format that includes the imaging findings, the probability of cancer, and the recommendation for the course of action [9]. To assist with the communication of mammographic interpretation, the *American College of Radiology* developed the *Breast Imaging Reporting and Data System* (BI-RADS) in 1992 to standardize reporting [10].

Recent studies regarding breast cancer focus on finding a number of specific clinical and imaging aspects for a vast array of molecular breast carcinoma immunophenotypes and genotypes, with a view to predicting more precisely the patient outcome and also identifying those patients that will respond to a specific therapy.

Materials and Methods

The study was conducted between January 2010 and December 2011 on 40 female subjects, all with invasive breast carcinoma. In their cases, the immunohistochemical exam resulted in an absence of estrogen hormone receptors (ER).

Clinicopathologic analysis

Age, identification method (palpation or screening mammography) and tumor state were recorded for all the patients. Those that took part in the study did not present distanced metastasis at the diagnosis moment and all patients were mammographically-investigated before the surgical procedure or before a biopsy. From the pathology reports, information on the histological type of breast carcinoma and the histological degree were extracted, based on the Nottingham system for breast carcinoma [11]. Moreover, information regarding the status of hormone (ER and PR) and oncoprotein HER2, were extracted from these reports.

Immunohistochemical and chromogenic *in situ* hybridization analysis

The immunohistochemical study was performed in the Pathology Department of the Emergency County Hospital of Craiova using the anti-ER antibodies (Dako Cytomation, Denmark, clone 1D5), anti-PR (Dako Cytomation, Denmark, clone PgR 636), and anti-HER2 (DakoCytomation, Denmark, polyclonal), and EnVision technique (Table 1).

Table 1 – ***Antibodies used for the immunohistochemical study***

Primary antibody	Clone	Dilution	Antigen retrieval	Incubation
Estrogen receptor	1D5	1:50	EDTA, pH 8, 20 minutes MW	one hour, at 37^0C
Progesterone receptor	PgR 636	1:50	EDTA, pH 8, 20 minutes MW	one hour, at 37^0C
HER2/neu	Polyclonal	1:250	Citrate, pH 6, 20 minutes MW	30 minutes, at RT

The signal was brown with membrane distribution for HER2/neu and nuclear for ER and PR. For scoring, only the invasive tumor was evaluated and the *in situ* area was excluded. In each determination, external control slides were included; the internal control was represented by normal glandular structure.

HER2/neu immunohistochemical staining assessment was according to the original *FDA* and new *ASCO/CAP* guideline recommendation [12]. According to this, scoring was done on a 0–3 scale. Specimens with HER2 3+ staining score were considered positive and had strong complete membrane staining in more than 30% of tumor cells. Specimens with HER2 0 and 1+ staining score were considered negative and had no or barely membrane staining in more than 10% of tumor cells. Specimens that showed an intermediate (borderline) score of 2+ (weak to moderate complete membrane staining in more than 10% of tumor cells or strong complete membrane staining in less than 30% of tumor cells) were considered equivocal. These specimens were assessed by chromogenic *in situ* hybridization using SPoT-Light® HER2 CISH Kit (Invitrogen Corporation) and only cases with gene amplification were considered positive. HER2 gene was considered amplified when we detected more that five signals/nucleus, or cluster of amplified signals/nucleus in >50% of tumor cells.

To quantify the hormonal status, we used the Allred score. This score is the sum of the proportion of marked cells (Table 2) and the medium intensity of the nuclear marking (Table 3). The tumors that had an Allred score ≤2 were considered negative, and the ones that had an Allred score >2 were positive.

Table 2 – ***Proportion score***

Proportion of positive cells	Proportion score
0	0
0–1%	1
1%–10%	2
10%–1/3	3
1/3–2/3	4
2/3–100%	5

Table 3 – ***Intensity score***

Intensity of the staining	Intensity score
Absent	0
Weak	1
Moderate	2
Strong	3

Image analysis

Mammograms of all patients were evaluated according to the *American College of Radiology Breast Imaging Reporting and Data System* [10]. The mammographic lesions were described as masses, masses with calcifications, calcifications clusters only, architectural distortion and focal asymmetries. The masses were evaluated for size, shape and margins and the calcifications were described in morphologic terms. The overall breast density was described as dense, heterogeneously dense, scattered, fibro-glandular or fatty.

Results

The 40 ER-negative female patients included in this study were aged between 25 and 88 years (mean age 51 years).

Regarding the histological type, the most ER-negative

infiltrative mammary carcinomas which were analyzed were classified as infiltrative ductal NOS, two (5%) were mucinous cases, two (5%) metaplastic and one (2.5%) lobular. Regarding the degree of differentiation, the 35 infiltrative ductal carcinomas were class 1 in three (8.57%) cases, class 2 in 10 (28.57%) cases and class 3 in 22 (62.86%) cases.

The immunohistochemical assessment for progesterone receptor (PR) showed that, out of the total of 40 female patients with estrogen negative mammary carcinoma selected for this study, 33 (82.5%) cases were PR-negative. The seven (17.5%) cases left were PR-positive but had a general low Allred score (three cases had a score of 3 and 4). A single case had an Allred score of 6. The immunohistochemical assessment for HER2/neu protein showed that 11 (27.5%) female patients were HER2-positive. Eight of 11 cases presented a score of 3+ to the IHC assessment and three cases had a score of 2+ but with HER2 gene amplification at CISH assessment.

The other 29 (72.5%) female patients were HER2-negative (17 cases scored HER2 0, seven cases scored HER2 1+ and five cases that scored HER2 2+ but without the HER2 gene amplification). Depending on the status of the HER2 oncoprotein, the female patients formed two subgroups: the ER-negative HER2-positive (11 patients) subgroup and the ER-negative HER2-negative subgroup (29 patients). Out of a total of 10 HER2-positive female patients, nine (81.81%) had PR-negative tumors and from HER2-negative patients, just 14 (48.27%) had PR-negative tumors. We have to mention that 24 (60%) of the patients had triple-negative breast cancer (with ER-negative, PR-negative and HER2-negative phenotypes).

Ten (90.9%) of the 11 patients that were part of the subgroup with ER-negative HER2-positive cancer had infiltrative ductal carcinoma NOS at the histological examination and one (9.1%) patient had infiltrating mucinous carcinoma grade 2. Out of the 29 patients that constituted the ER-negative and HER2-negative cancer subgroup, 25 (86.2%) had infiltrative ductal carcinoma NOS, one (3.45%) had infiltrative lobular carcinoma, one had mucinous carcinoma grade 2, and two (6.9%) had low-grade metaplastic carcinomas. The HER2-positive infiltrating mucinous carcinoma had a 2+ score at the immunohistochemical examination and after the CISH examination there was an amplification of HER2 gene.

Ductal invasive carcinomas NOS HER2-positive were, in two cases, moderately differentiated and in eight (80%) cases, faintly differentiated. No ductal invasive NOS first-degree carcinoma was HER2-positive. Ductal invasive NOS HER2 carcinomas were well-differentiated in three (12%) cases, moderately differentiated in eight (32%) cases and faintly differentiated in 14 (56%) cases.

Twenty-one ER-negative breast cancer patients have axillary lymph node metastases. Among them, seven (63.63%) had HER2-positive cancer and 14 (48.27%) presented with HER2-negative cancer and had axillary lymph node metastases. At presentation, the HER2-positive cancers were stage I in two (18.18%) cases, stage II in five (45.45%) cases, and stage III in four (36.36%) cases. The HER2-negative cancers were stage I in 11 (37.93%) cases, stage II in 10 (34.48%) cases, and stage III in eight (25.58%) cases. Thus, we noticed that the clinical stage was associated with HER2 status. HER2-positive cancers were more likely to be stage II or III than HER2-negative cancers (81.81% *vs.* 62.06%) (Table 4, Figures 1–5).

Tumors were detected by palpation in 16 cases and by screening in 24 cases. Subsequently, all patients had diagnostic mammographies before a surgical procedure and these were available for review (Table 5).

Mammograms of 11 patients in ER-negative HER2-positive tumors subgroup presented in two (18.18%) cases masses without associated calcifications, in six (54.54%) cases masses with associated calcifications, in two (18.18%) cases clusters of suspicious calcifications and in a single (9.1%) case, architectural distortion.

Mammograms of 29 patients in ER-negative and HER2-negative tumor subgroup presented in 14 (48.27%) cases masses without associate calcifications, in four (13.79%) cases, associate mass calcifications, in three (10.34%) cases, clusters of suspicious calcifications, and in one (3.45%) case architectural distortion. Focal asymmetries were detected in two (6.9%) cases, whereas in five (17.24%) cases the mammograms were normal.

The dimensions of the tumors were examined at the mammographic exam, resulting 0.6 up to 10.7 cm tumors, with a mean tumor size of 4.6 cm in the patients with HER2-positive cancer and 3.9 cm in those with HER2-negative cancer.

The mass shape of the eight cases ER-negative HER2-positive tumors with a mass was predominantly irregular (five cases, 62.5%), other two (18.18%) tumors being round/oval and one (12.5%) tumor being lobular. Among the 18 HER2-negative tumors with a mammographic mass, predominate the round/oval mass shape (nine cases, 50%). Six (33.33%) cases had irregular mass shape and three (16.66%) cases had lobulated aspect (Figures 6 and 7).

Table 4 – ***Histopathologic features in the study group***

Clinicopathologic features	HER2-positive, *n*=11 (%)	HER2-negative, *n*=29 (%)
Age [years]	48 (30–80)*	53 (25–88)*
Method of tumor detection		
Palpation	5 (45.45)	11 (37.93)
Mammography	6 (54.55)	18 (62.07)
Histologic type		
Infiltrating ductal carcinoma	10 (90.9)	25 (86.2)
Invasive lobular carcinoma	0	1 (3.45)
Infiltrating mucinous carcinoma (G2)	1 (9.1)	1 (3.45)
Metaplastic carcinoma (G3)	0	2 (6.9)

Clinicopathologic features	HER2-positive, *n*=11 (%)	HER2-negative, *n*=29 (%)
Histologic grade of infiltrating ductal carcinoma NOS		
Grade 1	0	3 (12)
Grade 2	2 (20)	8 (32)
Grade 3	8 (80)	14 (56)
Lymph node metastases	7 (63.63)	14 (48.27)
Progesterone receptor negative	9 (81.81)	14 (48.27)
Clinical stage		
Stage I	2 (18.18)	11 (37.93)
Stage II	5 (45.45)	10 (34.48)
Stage III	4 (36.36)	8 (27.58)

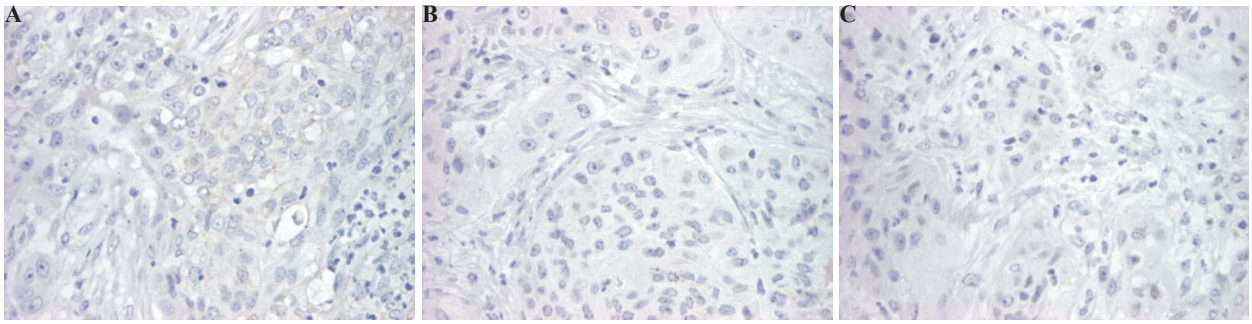

Figure 1 – ***Invasive ductal carcinoma NOS: (A) HER2/neu-negative (score 1+) (×200); (B) ER-negative (×200); (C) PR-positive (Allred score 3) (×200).***

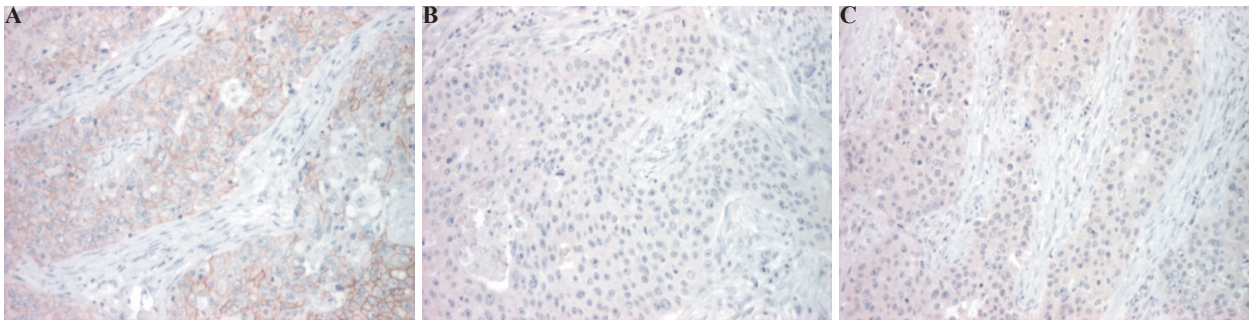

Figure 2 – ***Invasive ductal carcinoma NOS: (A) HER2/neu-equivocal (score 2+) (×100); (B) ER-negative (×100); (C) PR-negative (×100).***

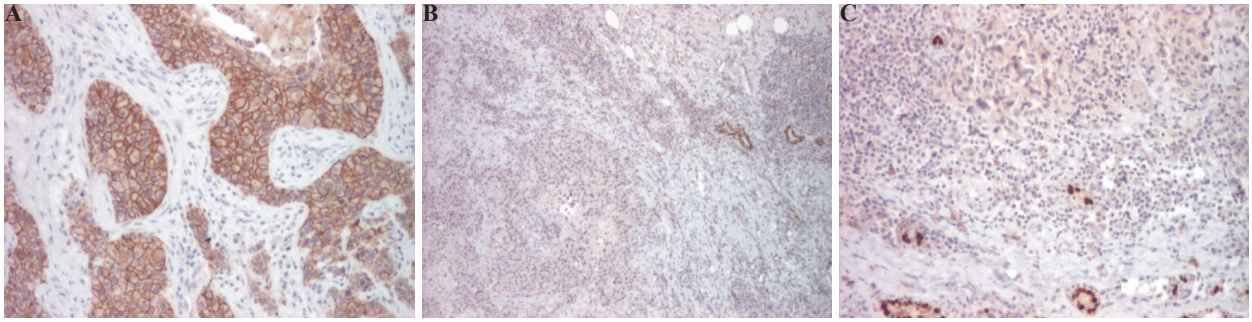

Figure 3 – ***Invasive ductal carcinoma NOS: (A) HER2/neu-positive (score 3+) (×40); (B) ER-negative, positive internal control (×40); (C) PR-negative, positive internal control (×40).***

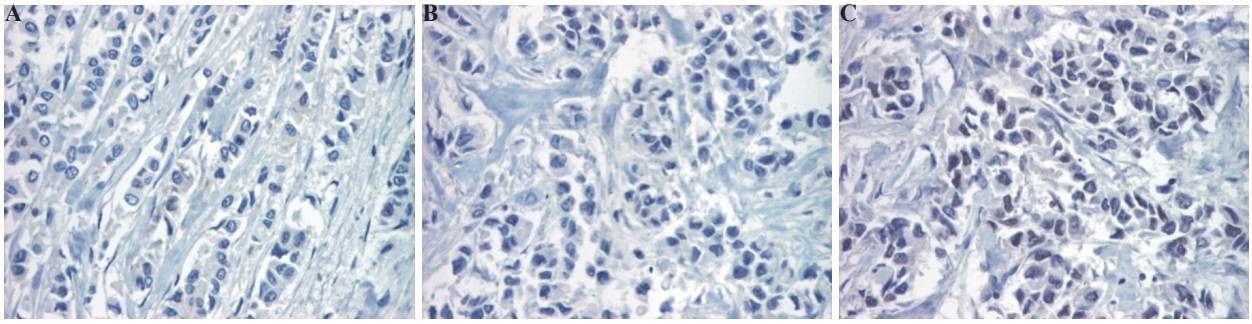

Figure 4 – ***Invasive lobular carcinoma NOS: (A) HER2/neu-negative (score 0) (×200); (B) ER-negative (×200); (C) PR-positive (Allred score 6) (×200).***

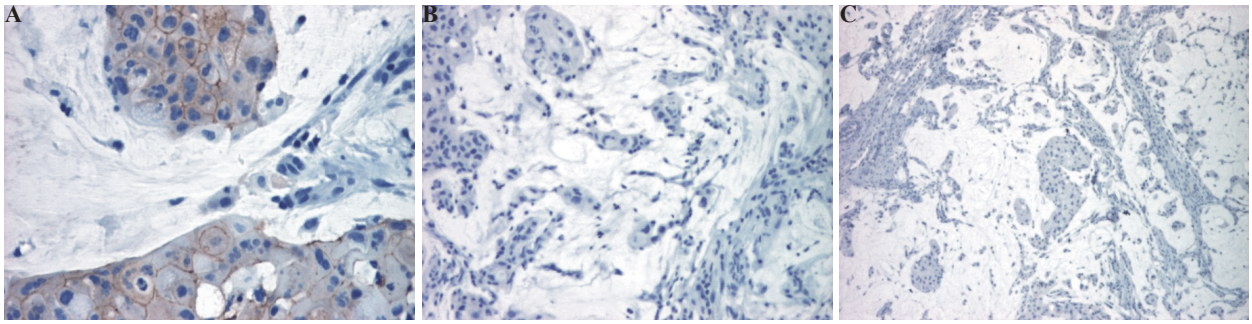

Figure 5 – ***Invasive mucinous carcinoma: (A) HER2/neu-equivocal (score 2+) (×200); (B) ER-negative, (×100); (C) PR-negative, (×40).***

Table 5 – ***Mammographic features in the study group***

Mammographic features	HER2-positive, *n*=11 (%)	HER2-negative, *n*=29 (%)
Mammographic finding		
Normal	0	5 (17.24)
Masses	2 (18.18)	14 (48.27)
Masses with calcifications	6 (54.54)	4 (13.79)
Calcification clusters only	2 (18.18)	3 (10.34)
Architectural distortion only	1 (9.1)	1 (3.45)
Focal asymmetries	0	2 (6.9)
Mean lesion size [cm]	4.6 (0.6–10.7)*	3.9 (1.3–9.5)*
Mass shape		
Round/oval	2 (25)	9 (50)
Lobulated	1 (12.5)	3 (16.66)
Irregular	5 (62.5)	6 (33.33)
Mass margin		
Circumscribed	0	4 (13.79)
Microlobulated	1 (9.1)	0
Indistinct	2 (18.19)	8 (27.58)
Spiculated	5 (45.45)	2 (6.9)
Breast density		
Dense	5 (45.45)	5 (17.24)
Heterogeneously dense	4 (36.56)	15 (51.72)
Scattered fibroglandular	1 (9.1)	7 (24.14)
Fatty	1 (9.1)	2 (6.9)
Suspicious calcifications		
Total	8 (72.72)	7 (24.14)
Pleomorphic	5 (62.5)	2 (28.57)
Punctate	2 (25)	2 (28.57)
Amorphous	1 (12.5)	1 (14.28)
Branching	0	1 (14.28)
Fine linear	0	1 (14.28)

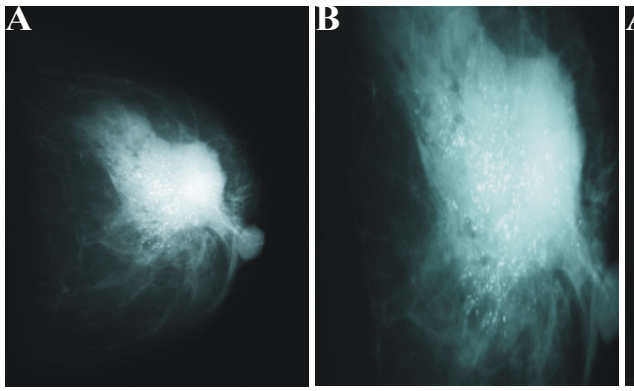

Figure 6 – ***Invasive ductal carcinoma HER2/neu-positive mammography: (A) Irregular shape mass, with spiculated margins and pleomorphic calcifications (left breast, mediolateral oblique view); (B) Detail for calcifications.***

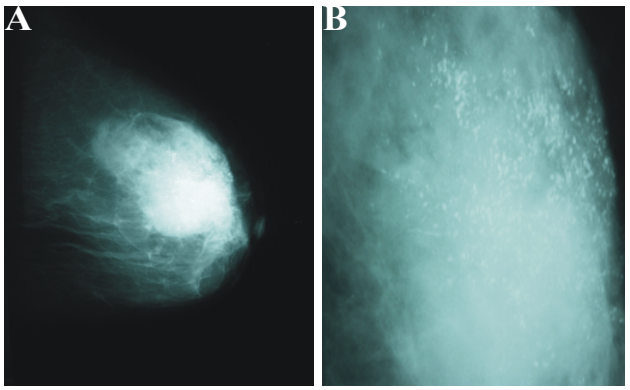

Figure 7 – ***Invasive ductal carcinoma HER2/neu-negative mammography: (A) Round/oval shape mass with indistinct margins and pleomorphic calcifications (right breast, mediolateral oblique view); (B) Detail for calcifications.***

The appearance of mammographic margins in the 11 ER-negative HER2-positive tumors was spiculated in the majority of cases (five cases, 45.45%), indistinct in two (18.19%) cases and microlobulated in one (9.1%)

case. The mass margins in the 29 ER-negative HER2-negative tumors were predominantly indistinct (eight cases, 27.58%). Four (13.79%) cases had circumscribed mass margins and only two (6.9%) cases had spiculated margins. Out of a total of 24 triple-negative tumors, only two (8.33%) cases had spiculated margin tumoral masses at the mammographic examination.

The overall breast density in the ER-negative HER2-positive cancers was dense in five (45.45%) cases, heterogeneously dense in four (36.36%) cases, scattered fibroglandular in one (9.1%) case and fatty in one (9.1%) case. In ER-negative HER2-negative cancers, the breast density was heterogeneously dense in 15 (51.72%) cases, scattered fibroglandular in seven (24.14%) cases, dense in five (17.24%) cases and fatty in two (6.9%) cases.

There were significant differences between the HER2 status and the presence of calcifications because 72.72% of the HER2-positive cancers and 24.14% of the HER2-negative tumors had associated calcifications. Regarding the type of calcifications, we find significant the association between HER2-positive cancers and pleomorphic calcifications (five cases, 62.5%). The three remaining HER2-positive tumors had pointed calcifications (two cases, 25%), and one case had amorphous calcification. Out of the seven HER2-negative tumors that presented calcifications, two (28.57%) cases had pleomorphic calcifications, two had pointed calcifications and in one (14.28%) case, we found amorphous, branching and fine linear calcifications.

Discussion

Estrogen receptor (ER) status is considered an important prognostic factor as well as a predictive factor for endocrine responsiveness in breast cancer [13–15]. According to the study of Abu-Hamar Ael-H *et al.*, in 2010, ER-negative disease is a poor risk factor for any type of recurrence, and the five-year OS for patients with ER-positive disease is 79.8% compared with 44.9% for those with ER-negative disease. This difference was statistically highly significant (p=0.0001). Also, the five-year systemic DFS is 72.1% in patients with ER-positive disease compared to 38.3% for those with ER-negative disease (p=0.0001) [16].

As far as the clinicopathological aspects of the ER-negative mammary carcinomas analyzed in this research, we have noticed a series of differences depending on the HER2 status. Thus, the subgroup of ER-negative carcinomas HER2-positive generally included carcinomas of high histological degree (80% *vs.* 56%), with receptors for absent progesterone in most of the cases (81.81% *vs.* 48.27%), which were followed by axillary lymph node metastases (63.63% *vs.* 48.27%) which were detected in advanced stages II/III (81.81% *vs.* 62.06) as compared to the subgroup of ER-negative carcinomas HER2-negative. It is worth mentioning that over half of mammary cancers analyzed in this research (24 female patients, 60%) had triple-negative breast cancer (with ER-negative, PR-negative, HER2-negative phenotypes). Triple-negative breast cancer represents a distinct subset of breast cancer that exhibits a more aggressive course as compared to other biological subtypes of cancer [17]. Patients with triple-negative breast cancer do not benefit from hormonal or trastuzumab-based therapies because of the loss of target receptors such as ER, PR, and HER2 [18].

Of the 16 female patients, the ER-negative patients with whom the detection of the mammary cancer was achieved by palpation, only 31.5% (five patients) had HER2-positive tumors, most of the patients 68.75% (11 cases) having HER2-negative tumors. Although most of these cases lacked receptors for progesterone, we can notice that, in this particular research, mammary cancers discovered through palpation did not have a higher rate of positivity for HER2 as compared to those discovered through mammographic screening.

Some researches indicate that the symptomatic breast cancers (*i.e.*, they noticed a mass at self-palpation or experienced breast discomfort) had a more aggressive and worse prognostic phenotype, with a higher percentage of c-erbB-2 positivity, higher percentage of ER and PR negativity, a higher proliferative index, and a higher grading comparative to those who underwent the imaging examinations as a check without experiencing any symptoms [19]. The authors of these researches, carried out on a high number of mammary cancers (1916 cases), even suggest that asymptomatic tumors are biologically different from their clinically presenting counterparts, thus confirming the hypothesis that progression towards greater malignancy may occur during the natural history of breast cancer. The results of these authors are also in agreement with the new breast cancer hypothesis formulated by Hellman S, according to whom breast cancer is a spectrum of diseases with different capacities for growth and metastasis, and the increased tumor volume necessary for clinical detection provides more clonogens available for metastasis and cause further progression of the malignant phenotype [20]. The authors concluded, if this is the case, screening allows cancers to be found at an earlier and probably less malignant stage of development, when they may not have achieved metastatic potential (as judged by their favorable pathological and biological features).

And yet, results are contradictory, thus Gibbs NM [21] found an association with the size but not with the modality of diagnosis. A positive significant association with c-erbB-2 was found by Rajakariar R and Walker RA [22], but Soomro S *et al.* [23] found only a trend for c-erbB-2 negativity in impalpable *vs.* palpable tumors in a screened population. Tweedie E *et al.* [24] did not find any difference in the frequency of c-erbB-2 positivity between screened and unscreened, or palpable and occult tumors, respectively. Some authors have failed to find any association between the modality of diagnosis and the markers of aggressiveness [25].

The overall mammographic breast density did not show significant differences in negative ER patients depending on HER2 oncoprotein status. Thus, high mammographic breast density was seen in 85% of cases of ER-negative HER2-positive subgroup and in 69% of the ER-negative HER2-negative subgroup. However, if it is to detail, breast density in the case of ER-negative HER2-positive mammary tumors was generally dense

(45.45% of the cases), while in the case of ER-negative HER2-negative tumors was generally heterogeneously dense (51.72% of cases).

Mammographic density, a quantitative measure of connective and epithelial tissue in the breast, is a strong risk factor for breast cancer [26] and is commonly represented as the percentage of total breast tissue on mammogram that is dense. Women with high percentage mammographic density are four to six times more likely to develop breast cancer compared with those with very low density [26].

Given that mammographic density is linked to hormone-related factors such as menopausal status and use of post-menopausal hormone therapy [27] and tamoxifen [28], one might expect it to be predominantly associated with luminal A (ER-positive, PR-positive, HER2-negative) breast tumors. However, one study has shown that high mammographic density is a strong risk factor for both ER+ and ER- breast cancer [29]. Furthermore, in another study, high density was not associated with HER2 status [30], these results being similar with those achieved by us in this research.

On the mammography of female patients with ER-negative mammary carcinomas we have noticed that tumors of patients from the subgroup with ER-negative HER2-positive carcinomas appear more frequently as irregular tumoral masses (62.5% *vs.* 33.33%) as compared to tumors of female patients included in the subgroup with ER-negative HER2-positive carcinomas which appear more frequently as tumoral masses of round/oviform shape (50% *vs.* 25%). Mean size of mammographically detected tumors was higher in the case of ER-negative HER2-positive cancers as compared to ER-negative HER2-negative cancers (4.6 cm *vs.* 3.9 cm).

The appearance of margins of tumoral masses detected on the mammographic examination has been predominantly spiculated in the case of ER-negative HER2-positive tumors (45.45% of cases), while ER-negative HER2-negative tumors have generally shown indistinct mass margins (27.58% of cases). Also, there was a significant difference between the HER2 status and the presence of calcifications in the ER-negative analyzed cancers. 72.72% of the HER2-positive cancers and only 24.14% of the HER2-negative tumors had associated calcifications. Regarding the type of calcifications, we find significant association of the HER2-positive cancers with pleomorphic calcifications (62.5% of cases). Thus, 62.5% of HER2-positive tumors have associated pleomorphic calcifications on mammography, while only 28.5% of HER2-negative tumors have associated this morphological type of calcifications on mammography. These results are in accordance with those of Wang Y *et al.*: lesion margins on mammograms (p=0.028) and sonograms (p=0.023), calcifications on mammograms (p=0.003), and clinical cancer stage at diagnosis (p=0.029) were significantly associated with HER2 status. In contrast to ER-negative HER2-negative tumors, ER-negative HER2-positive tumors were more likely to have spiculated margins (56% *vs.* 15%), be associated with calcifications (65% *vs.* 21%), and be detected at a higher cancer stage (74% *vs.* 57%) [31].

Conclusions

Compared to ER-negative HER2-negative breast cancers, ER-negative HER2-positive breast cancers were more likely to be high-grade tumors, with negative progesterone receptors, associated with lymph node metastasis, and are detected at a higher cancer stage (II/III). Regarding the mammographic features, the ER-negative HER2-positive breast cancers are more likely to be irregular masses, with spiculated margins, associated with pleomorphic calcifications. Comparatively, ER-negative HER2-negative tumors have been more frequently round/ovariform shaped masses with indistinct margins and have shown a great diversity of morphological types of calcifications. Correlations between some imagistic aspects and clinical aspects and the expression of biomarkers from mammary cancers can precociously suggest the biological features of these tumors, being able to guide through their evolution and prognostic and helping in identifying female patients with invasive mammary carcinoma, which will reply to an aimed therapy.

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