Dystrophic Large Calcification in Breast Cancer

CORINA LUPASCU URSULESCU[1,2], MANUELA URSARU[1,2*], DELIA CIOBANU[1,3], DRAGOS NEGRU[1,2], CRISTIAN LUPASCU[1,4]

[1]Grigore T.Popa University of Medicine and Pharmacy Iasi, 16 Universitatii Str., 700115, Iasi, Romania

[2]Sf. Spiridon Emergency Hospital, Department of Radiology, 1 Independentei Blvd.,700111, Iasi, Romania

[3]Sf. Spiridon Emergency Hospital, Department of Pathology, 1 Independentei Blvd.,700111, Iasi, Romania

[4]Sf. Spiridon Emergency Hospital, Surgical Unit 2, 1 Independentei Blvd., 700111, Iasi, Romania

There are well established diagnostic criteria for calcifications detected on mammography which allows the division into: benign intermediate concern and higher probability of malignancy according to the morphology. Large calcifications are usually associated with benign breast conditions. We report three cases of breast cancer with large dystrophic calcification on imaging studies (mammography, ultrasound, computed -tomography) and histopatology displayed into the tumor as well as into the tributaries lymph nodes.

Keywords: calcifications, breast cancer, imaging

Breast cancer typically associates calcification [1]. Up to 50 % of all non-palpable breast cancers are detected through microcalcifications on mammography, whereas up to 93 % of cases of ductal carcinoma in situ (DCIS) present microcalcifications [1]. Breast cancers presenting with microcalcifications are more often associated with lymph node invasion and HER-2 positivity [1,2], which results in a poorer prognosis.

Breast calcifications can be classified at the molecular level in two different types: type I calcifications composed of calcium oxalate (CaOx), and type II calcifications composed of calcium phosphate, mainly hydroxyapatite (CaP) [1]. CaOx crystals have been associated both with carcinomas (invasive as well in situ lesions) and with benign cystic breast lesions [1]. Oxalate is an organic dicarboxylate presenting as free oxalic acid, as soluble salts such as sodium or potassium oxalates, or as insoluble salts such as calcium oxalate crystals. It is an inert metabolic end product because mammalian cells cannot metabolize it [1].

Free oxalate has a marked carcinogenic effect, inducing proliferation of MCF-7 and MDA-MB231 breast cancer cell [1].

Radiologically, calcifications can be divided into: benign; intermediate concern; and higher probability of malignancy according to the morphology [3,4]. Microcalcifications are often associated with breast cancer, identified both inside breast lesion as well as into the tributary lymph nodes [5,6]. Large calcifications (larger than 1 mm) are usually associated with benign breast conditions, as vascular, infection, fibrocystic disease, trauma, surgery, previous radiation therapy [3,4, 7-9]. The specificity of this type of calcification is reported up to 100% for benign breast conditions [3, 4]. Large calcifications associated with breast cancer were scarcely reported.

The aim of this report is to present our experience of dystrophic large calcifications associated with palpable breast cancer.

Experimental part

Material and Methods

From January 2014 to December 2015, a population of 1380 female patients underwent breast imaging in our hospital, as a part of screening program for breast cancer or of diagnostic protocol for palpable breast cancer. The database was searched for patients with large calcifications associated with breast carcinoma. Three patients (0.2%, mean age 59.66, range 54-69) with palpable breast mass presented large calcifications on imaging studies, meeting the criteria for this study.

The details of patients with breast cancer and large calcifications are summarized in table 1.

	Age	Location of palpable mass	Location of calcifications			Type of operation
			Breast tissue	Breast cancer	Lymph nodes	
Case no 1	69	right	1	1	0	right radical mastectomy, axillary lymphadenectomy
Case no 2	54	right	1	1	1	right radical mastectomy axillary lymphadenectomy
Case no 3	56	left	0	1	1	biopsy

Table 1
PATIENTS' CHARACTERISTICS

***** *email: manuelaumf@yahoo.com ;Phone: (+40)742397531*

Results and discussions

Case no.1

Sixty-nine-old female presented with palpable nodule in the right breast. Personal medical record includes fibrocystic breast disease with hormone therapy for two years. Ultrasound identified a hypoechoic mass in the lower right quadrants with acoustic shadows inside, 25 mm in the maximum diameter. Enlarged, hypoechoic right axillary lymph nodes were also noted. Thoracic and abdominal CT was performed to exclude distant metastases (fig. 1). The patient was referred to surgery and a right radical mastectomy was performed.

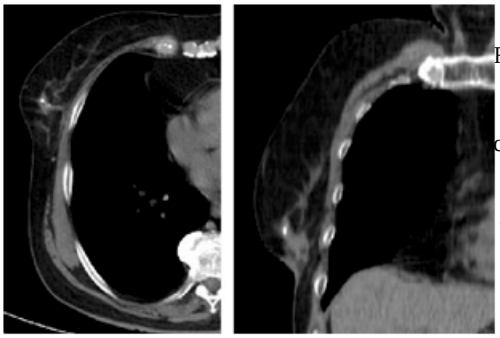

Fig.1. Computed-tomography: Invasive lobular carcinoma on the right breast disclosing large \calcification (> 1 mm)

Histopathology identified invasive lobular carcinoma and areas of lobular carcinoma in situ (LCIS), associated with rich hyaline sclerotic tissue and hyperelastosis. Coarse dystrophic highly hematoxylinophilic calcification was identified in areas of hyaline sclerotic tissue (fig. 2.a-d). Additional fibrocystic changes were identified in the mastectomy specimen. Six of 15 resected lymph nodes were positive for metastases of lobular carcinoma on immunohistochemical studies. No calcification was identified in axillary lymph nodes. Tumour phenotype was realized to facilitate the adequate oncological treatment and is presented in table 2. TNM stage was pT2N2a –G2.

Patient no.2

Fifty-four-old female presented with palpable mass in the right breast, with skin retraction and ulceration. Familial and personal medical records were unremarkable. Imaging work-up included ultrasound, mammography and CT, revealing the ill-defined mass in the right breast, bilateral axillary lymph nodes, and right supraclavicular lymph nodes. Large calcifications were identified in the breast mass, as well as in the ipsilateral axillar lymph nodes (fig. 3). CT showed no distant metastases. The patient was referred to surgery and a right mastectomy with axillary

Tumor phenotype features		Patient no 1	Patient no 2	Patient no 3
Elston -Ellis score	tubular differentiation	3	3	3
	nuclear pleomorphism	2	3	2
	mitotic activity	1	2	1
	Total	6 = **G2**	8 = **G3**	6 = **G2**
Estrogen receptors	percentage	100	50	95
	intensity score	3	2	3

Table 2
TUMOR PHENOTYPE

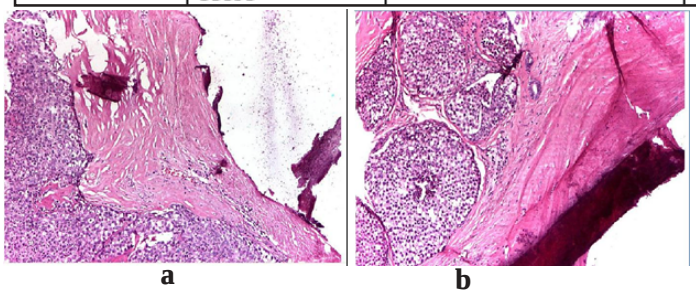

Fig. 2.a. In situ lobular carcinoma with hyaline sclerotic stroma and massive dystrophic calcifications, HE, x 4. b. In situ and invasive lobular carcinoma with rich hyaline sclerotic stroma and massive dystrophic calcifications, HE, x 4

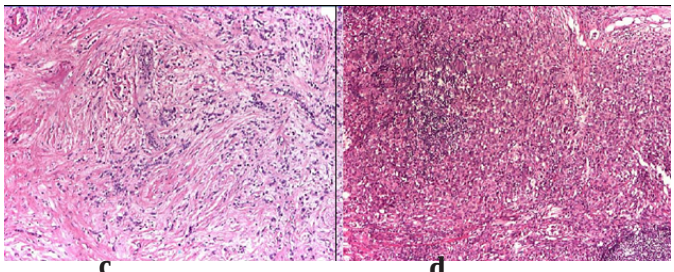

Fig. 2c. Invasive lobular carcinoma with desmoplastic stroma, no calcification, HE, x 4. d. Lymph node metastasis from lobular carcinoma of the breast, HE, x 4

Fig. 3. Computed tomography –invasive carcinoma NST of the right breast with large calcifications into the tumor and lymph nodes

lymphadenectomy was performed.

Histopathology identified invasive carcinoma NST, poorly differentiated, with infiltration and ulceration of the skin, and infiltration of pectoral muscle. Eleven of 12 resected lymph nodes were positive for metastases of ductal carcinoma. Multiple coarse dystrophic calcifications were identified into the tumour, nearby tumour cells, into the areas of hyaline sclerosis of the stroma and inside areas of comedocarcinoma with necrosis (fig. 4.a-f). Calcifications were also noted in axillary lymph nodes, corresponding to tumoral emboli inside capsular vessels (associated with areas of necrosis) and in peritumoral areas of hyaline sclerosis. Tumour phenotype is presented in table 2. TNM stage was pT4bN3a-G3.

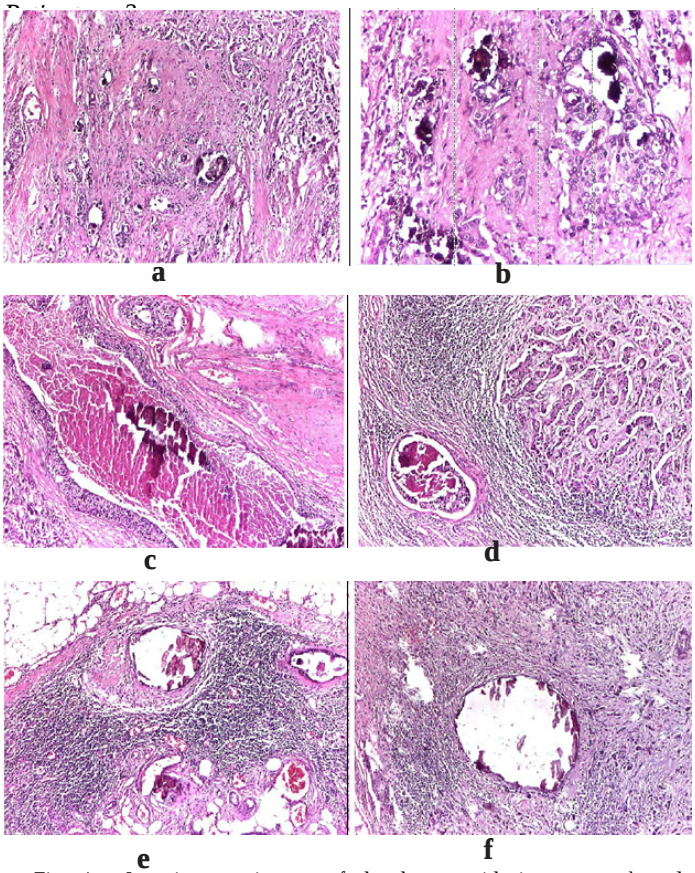

Fig. 4.a. Invasive carcinoma of the breast with intratumoral and stromal calcifications, HE, x 4. b.Stromal and peritumoral calcifications, HE, x 10 c. Comedocarcinoma with dystrophic calcifications, HE, x 4. d. Metastasis of carcinoma with dystrophic calcifications into the vascular embolus, HE, x 4. e. Lymph node metastasis with dystrophic calcifications, HE, x 4. f. Large dystrophic calcification into the lymph node, HE, x 10

Fifty-six-years old female, without significant medical history, presented with palpable mass into the left breast. Mammography identified large calcifications inside breast lesions as well as into the ipsilateral axillary lymph nodes.

Large lymph nodes calcifications and liver metastases were identified on CT (fig.5). Image-guided percutaneous core-biopsy was performed. Histopathology identified mucinous carcinoma with hypercellular areas and massive coarse calcifications in areas of hyaline sclerosis. TMN staging was cT4bN1aM1 –G2.

The BI-RADS calcifications of calcifications included [3]:

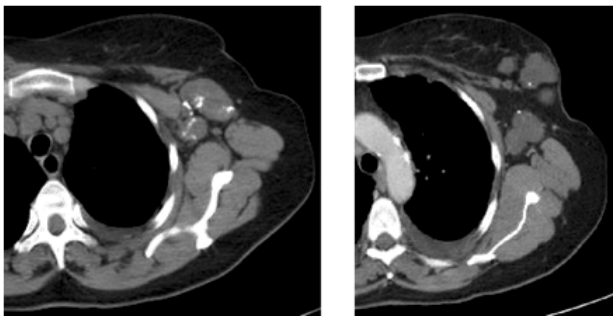

Fig. 5. Computed tomography - Mucinous carcinoma of the left breast with massive coarse calcifications into the breast lesion and axillary lymph nodes

-Typically benign: Skin calcifications, vascular calcification, coarse (popcorn) calcification, large rod like calcification, round calcifications, lucent center calcification, eggshell or rim calcification, milk of calcium calcification, suture calcification, dystrophic calcification and punctate calcification.

-.Intermediate concern calcifications: amorphous or indistinct calcifications or coarse heterogeneous calcifications.

-Higher probability of malignancy: fine pleomorphic calcifications (granular) and fine linear, or fine linear branching (casting) calcifications.

Therefore, large calcifications are atypical rare features of breast cancer. Three different histopathological types were identified in our cases: invasive carcinoma NST, invasive lobular with lobular carcinoma in situ, and mucinous carcinoma. Calcifications are described in these types of carcinomas with different incidence (90-95% of lobular carcinoma in situ, 30-40% of NST invasive breast carcinoma, 4 -24% of invasive lobular carcinoma, and 3-4% of mucinous carcinoma) [1, 10, 11]. Ductal carcinoma in situ and invasive duct carcinoma may be associated with large irregular, rod or V shaped, pleomorphic or branching type calcifications that follow the distribution of the duct [7, 10]. Macrocalcifications were identified in our cases inside areas of hyaline sclerosis or tumour necrosis only (1 case) or both into the tumour and axillary lymph nodes (2 cases). Dystrophic calcifications were described in areas of necrosis (particularly comedo necrosis of high grade ductal carcinoma in situ). Two mechanisms are involved in the pathogenesis: initiation and propagation, both either intra- or extra- cellular, with crystalline calcium phosphate being the ultimate end product [4].

All patients were investigated by mammography, ultrasound and MDCT and calcifications were identified by all of these methods. While mammography has a higher sensitivity for calcifications located into the breast, CT

identified calcifications regardless of their location. Even ultrasound identified calcifications in the lymph nodes, although ultrasound has lower sensitivity (40-50%) compared to mammography (99-100%) or CT (90-100%) in identifying calcifications [12-15].

Immunohistochemical assays revealed in all 3 cases positive hormonal receptors and negative Her 2 neu.

Although one patient had a history of benign fibrocystic condition, macrocalcifications were not associated with this type of lesion.

Conclusions

Large dystrophic calcifications, although not typical for breast cancer, can be identified in areas of hyaline sclerosis into the tumour or into the tributary lymph nodes. Assessment of calcification in breast lesions requires correlation with clinical and other imaging findings. While the calcifications associated with malignancy usually have a typical appearance, some malignancies show atypical calcification patterns.

References

1.CASTELLARO, AM., TONDA, A., CEJAS, HH., FERREYRA, H., CAPUTTO, BL., PUCCI, OA., GIL, GA. BMC Cancer, 15, 2015, p. 761

2.WANG, X., CHAO, L., CHEN, L., TIAN, B., MA, G., ZANG, Y., ET AL. J Digit Imaging, 21, nr. 2, 2008, p. 170–176.

3.D'ORSI, CJ., SICKLES, EA., MENDELSON, EB., MORRIS, EA., ET AL. ACR BI-RADS® Atlas, Breast Imaging Reporting and Data System. Reston, VA, American College of Radiology; 2013

4. TSE, GM., TAN, PH., PANG, AL., TANG, AP., CHEUNG, HS. J Clin Pathol., 61, nr. 2, 2008, p:145-51.

5.LE GAL, M., CHAVANNE, G., PELLIER, D. Bull Cancer, 71, 1984, p. 57-64.

6.HAGAY C, CHEREL P, DE MAULMONT C, OOHIOUN O, NODIOT P, PLANTET MM. J Le Sein, 11, nr. 1-2, 2001, p. 79-99.

7.TSE, GM., TAN, PH., CHEUNG, HS., CHU, WC., LAM, WW. Breast Cancer Res Treat., 110, nr.1, 2008, p. 1-7.

8. FRIEDRICH, M., SICKLES, EA. Radiological Diagnosis of Breast Diseases. Springer Verlag-Berlin-Heidelberg, 2000, p. 299-318.

9.BASTARRIKA, G., PINA, L., VIVAS, I., ELORZ, M., SAN JULIAN, M., ALBERRO, J. Eur. Radiology, 11, 7, 2001, p. 1195-1197.

10. BAE, MS., MOON, WK., CHANG, JM., CHO, N., PARK, SY. Breast European Radiology, 23, nr. 8, 2013, p. 2072-2078.

8

11.HOFVIND, S., IVERSEN, BF., ERIKSEN, L., STYR, BM., KJELLEVOLD, K., KURZ, KD. Acta Radiol., 52, nr. 5, 2001, p. 481-7.

12.BALU-MAESTRO, C., BRUNETON, JN., MELIA, P., CHAUVEL, P., AVIOTTI-CASPERONI, A. Eur J Ultrasound, 1, 1994, p. 247-250.

13.NAGASHIMA, T., HASHIMOTO, H., OSHIDA, K., NAKANO, S., ET AL. Breast Cancer, 12, 2005, p. 216-220.

14.GUFLER, H., BUITRAGO-TELLEZ, CH., MADJAR, H., ALLMANN, KH., UHL, M., ROHR-REYES, A. Acta Radiol, 41, 2000, p. 217-221.

15.MOON, WK., IM, JG., KOH, YH., NOH, DY., PARK, IA. Radiology; 217, 2000, p. 849-854.

Intrat in redactie:14.12.2016