Cukurova Medical Journal

Davetli Yazı / Review Article

A Pathologists Purview of Breast Calcifications

Patolog Gözüyle Meme Kalsifikasyonları

Smita Sankaye[1], Sushil Kachewar[1]

[1]Rural Medical College, PIMS(DU), Loni, Ta-Rahata, Ahmednagar Maharashtra, INDIA-

Cukurova Medical Journal 2014;39(3):.413-421.

ABSTRACT

Accumulation of calcium or calcium salts in breast parenchyma; where it does not belong naturally leads to an abnormality known as Breast Calcification. When such calcifications occur due mineral deposits in individuals with normal calcium levels, these are called as dystrophic calcifications. As against this, metastatic calcification is the term used when calcification occurs in otherwise normal tissue with elevated calcium levels.

Although calcifications in breasts are reported with breast cancers; they can also be seen in benign conditions. They cannot be directly seen by the naked eye. Although sonomammography can demonstrate them many times; often the microcalcifications can go un-noticed. X-ray mammography is the best diagnostic tool to show them reliably; on which they appear as white specks or dots. This article puts forth a Pathologist`s purview of breast calcifications.

ÖZET

Meme parenkimasında biriken kalsiyum ya da kalsiyum tuzları doğal olmadığı gibi Meme Kalsifikasyonu olarak bilinen anormalliğe yolaçar. Böyle kalsifikasyonlar normal kalsiyum düzeyleriyle mineral depolarında ortaya çıktığı zaman bunlara distrofik kalsifikasyon adı verilir. Bundan farkli olarak normal dokularda kalsiyum düzeyinin artmasıy içinse Metastatik Kalsifikasyon terimi kullanılır.

Meme kalsifikasyonları meme kanseriyle birlikte bildirilmelerine rağmen iyi huylu olarakda görülebilir. Bunlar çıplak gözle farkedilemeyebilir. Sonomamografiyle bir çok kez görülmelerine rağmen, mikrokalsifikasyonlar farkedilmez. Bu durumlar için en iyi tanı X-RAY Mamografidir ki burada beyaz leke ya da nokta şeklinde görülürler. Bu makalede bir Patologun Meme Kalsifikasyonuyla ilgili görüşüne yer verilmiştir.

INTRODUCTION

No calcifications are present in normal human breast. But when calcium or calcium salts get deposits inside the mammary tissue, the term Breast calcifications is employed.

T he onset of breast calcifications is in the form of microscopic calcium deposits, which represent changes of ageing due to wear and tear in the breast as a woman gets older. Different patterns of calcifications have been reported that may signify the presence of cancer[1,2,3,4].

These calcifications are not visible to naked eye. X- ray mammograms enable us to see them by the images of the soft tissues of breast at high resolution; on which they appear as tiny white specks[5]. Sonomammography may miss the micro calcifications. A pathologist can see calcific deposits under a microscope only when representative breast tissue is biopsied.

Breast Calcifications[6-11]

Depending upon their appearance on x-ray mammography, these calcifications are divided into two types:

1) Macrocalcifications[8,9] are bigger bits of calcium, occuring in chunks or groups and are not usually seen in breast cancer. Figure 1 shows macrocalcifications in a benign breast lesion like fibroadenoma on X-ray mammography. Figure 2 shows this lesion on the sono-mammography as a multi lobulated hyperechoic lesion with posterior acoustic shadowing. Masses diagnosed as probably benign on ultrasound also need periodic follow up and tissue diagnosis for confirmation[11].

2) Microcalcifications[5] are very tiny bits of calcium, and may be seen in clusters or in patterns like circles or lines and are associated with extra cell activity in breast tissue. Usually the extra cell growth is not cancerous, but sometimes tight clusters of microcalcifications can indicate early breast cancer. Figure 3 shows microcalcifications in a malignant breast cancer proved on biopsy as intraductal carcinoma of breast (DCIS).

Calcification in breast lesions: A radio-pathological correlation

A pathologist`s perspective on breast calcification[12,13] throws some light on the occurrence and different appearances of breast calcifications. It is believed that the morphology and distribution of the calcification are related to the histology of the lesions.

Vascular Calcifications

These occur due to calcification of the media of small arteries common, particularly in older patients. These are usually recognized as vascular from the X-ray mammographic appearances of tubular radio-opacities having tram-track like appearance. This calcification is also seen on pathology sections as in Figure 4. A study[14] has shown regression of vascular calcification in a patient treated with cinacalcet.

On mammography, multiple linear radio-opacities indicative of vascular calcifications in a patient of chronic renal failure secondary to tubule-interstitial disease that developed secondary hyperparathyroidism; were found to regress after adding cinacalcet to her treatment with vitamin D derivatives and phosphate-binding agents, which resulted in a good control of mineral metabolism. Follow up mammography also showed regression of the vascular calcification. Hence it is believed that cinacalcet may have potential for regression of vascular calcification in patients with secondary hyperparathyroidism[14].

Duct ectasia

Calcification in breast can also be seen in ecstatic ducts. These are coarse and luminal are shown in Figure 5.

Calcification in old fat necrosis

Coarse stromal calcifications in an area old fat necrosis are shown in Figure 6.

Old fibroadenomas

Old sclerosed fibroadenomas show coarse calcifications. They form a common cause of calcifications in the setting of screening mammography. Radiologically if the underlying rounded mass lesion is not obvious one may be confused. These calcifications are usually coarse and stromal. It is uncommon in the more cellular fibroadenomas seen in younger patients.

Malignant Microcalcifications

Calcification in DCIS may occur with any grade. Finer calcifications are associated with low grade DCIS. Coarse luminal calcifications associated with comedo DCIS. Periductal stromal calcification may be seen alone or in groups as well.

As a result of the widespread utilization of screening mammography a shift has been seen in the stage of breast cancer diagnosis in the United States of America[15]. Out of the newly diagnosed breast cancer cases of ductal carcinoma in-situ; the diagnosis is made, in at least 90% of patients, with mammography. Barely 10% have a palpable mass. Often magnification of mammographic imaging depicts calcifications in a better form. Round and uniform shapes are more likely to be

benign, while linear and heterogeneous morphologies are associated with Ductal Carcinoma in situ (DCIS).

DCIS is now diagnosed more as more women opt for screening mammography[16,17]. There are specific mammographic findings most associated with shapes (amorphous, fine and coarse pleomorphic, and fine linear) and distributions (linear and segmental) of the calcifications that permit a reasonable sensitivity for detection of DCIS without an unreasonable decrease in specificity. It must however be remembered that some DCIS may never progress to invasive disease, at this time, we cannot make that separation.

Thus DCIS represents a challenge in mammographic screening due to its unknown progression into invasive cancer. In a study from Norway[17]; although DCIS presented overlapping groups of morphology, fine pleomorphic and fine linear branching calcifications with grouped and segmental distributions were associated with high grade DCIS. Seeking for further knowledge that allows separation of non-high grade from high grade DCIS has to continue to improve the quality of mammographic screening.

Hence mere clustering of calcification alone may not be an accurate predictor for malignancy, but when there are associated features like pleomorphism, branching, architectural distortion, and associated mass or density, the predictive value for malignant increases. Hence, adequate sampling of calcification in the biopsy is crucial in the management of patients. Needle core biopsy or mammotome biopsy achieves satisfactory calcification retrieval. To minimize the potential of a false negative investigation in a benign biopsy that fails to identify the calcifications visible in the mammography, further evaluation or cutting of the histologic block is recommended.

It can therefore be concluded that now-a-days breast biopsies are commonly performed for abnormal calcifications seen on mammography. In a study to determine the composition of calcifications[18] it was concluded that calcium phosphate was typically medium to high density, whereas calcium oxalate was characterized as amorphous, low to medium density. Other low-density calcifications were almost always benign, unless pleomorphic in shape. Calcium phosphate which is the predominant form of calcium seen in breast tissue is frequently associated with malignancy; whereas calcium oxalate has been exclusively associated with benign lesions. Hence it is proposed that if mammography could distinguish calcium phosphate from calcium oxalate, biopsy could be avoided in some patients.

As establishing correlation between histologic and imaging findings is required for accurate diagnosis; there is now an appreciable shift from surgical to image-guided core needle biopsies (CNBs). Currently, there are no standardized multidisciplinary protocols for evaluating such lesions. In recent attempts[19] to correlated histologic and radiologic findings in mammographically detectable calcified lesions in CNBs using specially designed Path/Rad Tissue Trays (patent pending, University of Kansas) ; images of CNBs with calcifications are marked by the radiologists and sent to the pathologist along with the biopsies. This group has advocated a systematic approach to standardize reporting of calcifications. It is believed that the use of Path/Rad Tissue Trays would create a better level of concordance between pathologists and radiologists. Thereby it would improve diagnostic reliability, encourage communication between pathologists and radiologists, and minimized false diagnoses and/or delays in cancer diagnosis.

In a study from Japan[20], mammographic findings were evaluated with an emphasis on mass shape, margin, density, calcification, and the presence of architectural distortion; these findings were correlated with histopathological characteristics such as intrinsic subtype, histological grade, lymphovascular invasion, and

the Ki-67 labeling index. There was significant differences between between tumors with a punctate and amorphous or pleomorphic calcification shape (P = 0.030 and 0.038). Significant differences were noted in the mammographic features of different primary breast cancer subtypes.

It has now been proved that ryanodine receptor 3 gene (RYR3), which encodes a large protein that forms a calcium channel, is important for the growth, morphology, and migration of breast cancer cells[21]. A putative binding site for microRNA-367 (miR-367) exists in the 3'UTR of RYR3, and a genetic variant, rs1044129 A→G, is present in this binding region. Also, miR-367 regulates the expression of a reporter gene driven by the RYR3 3'UTR and the regulation is affected by the RYR3 genotype. A thermodynamic model based on base pairing and the secondary structure of the RYR3 mRNA and miR-367 miRNA showed that miR-367 had a higher binding affinity for the A genotype than for the G genotype. The rs1044129 SNP was genotyped in 1,532 breast cancer cases and 1,600 healthy Chinese women. The results showed that compared with the AA genotype, G was a risk genotype for breast cancer development and was also associated with breast cancer calcification and poor survival. Thus, rs1044129 is a unique SNP that resides in a miRNA-gene regulatory loop that affects breast cancer risk, calcification, and survival.

Thus calcifications in breast are very important for diagnosing breast lesions. Therefore, recently high-resolution computed tomography of single breast cancer microcalcifications has been attempted in vivo[22]. As microcalcification is a hallmark of breast cancer and a key diagnostic feature for mammography a robust animal model of breast cancer microcalcification was described. It was hypothesized that high-resolution computed tomography (CT) could potentially detect the genesis of a single microcalcification in vivo and quantify its growth over time. By optimizing acquisition and reconstruction parameters, they were able to image a single 300 μm × 100 μm hydroxyapatite crystal. In a rat model of breast cancer, the genesis of a single microcalcification in vivo was detected and its growth was followed longitudinally over weeks. Thus, this study provides an in vivo "gold standard" for the development of calcification-specific contrast agents and a model system for studying the mechanism of breast cancer microcalcification.

Thus, as shown in this pathologist's purview, mammographic features of calcifications are associated with clinico-pathological characteristics in invasive breast cancer[23]. Hence these can be used as the pathological and mammographic prognostic factors for screen detected cancers as has been shown in a multi-centric randomized, controlled trial[24].

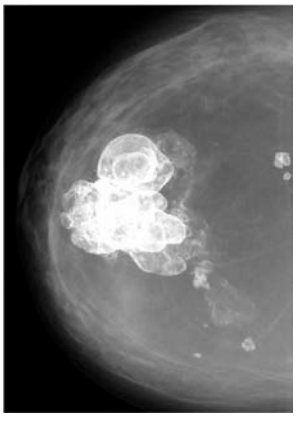

Figure 1. Macrocalcifications in a benignbreast lesion like fibroadenomaare seen as popcorn calcifications on x-ray mammogram.

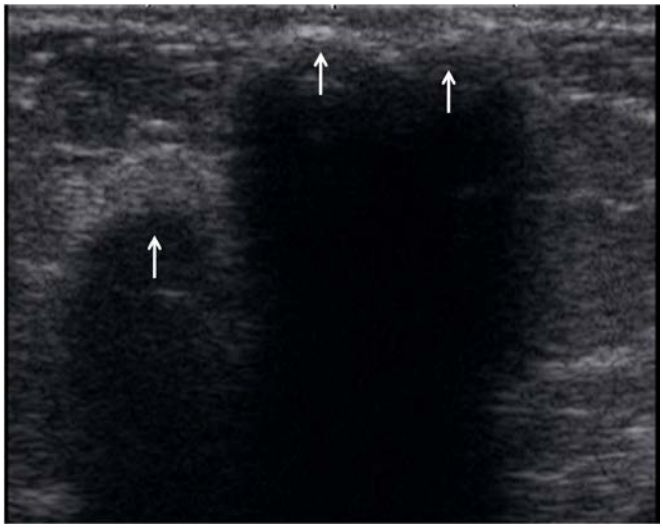

Figure 2. Sono-mammography shows this calcified benign mass as a multi lobulated hyperechoic lesion with posterior acoustic shadowing.

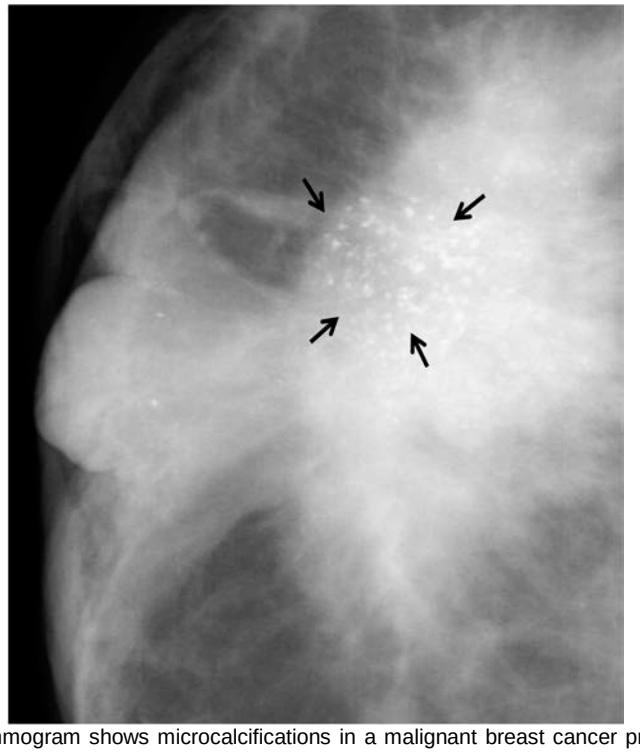

Figure 3. X-ray mammogram shows microcalcifications in a malignant breast cancer proved on biopsy as intraductal carcinoma of breast. These were not visualized on ultrasound.)

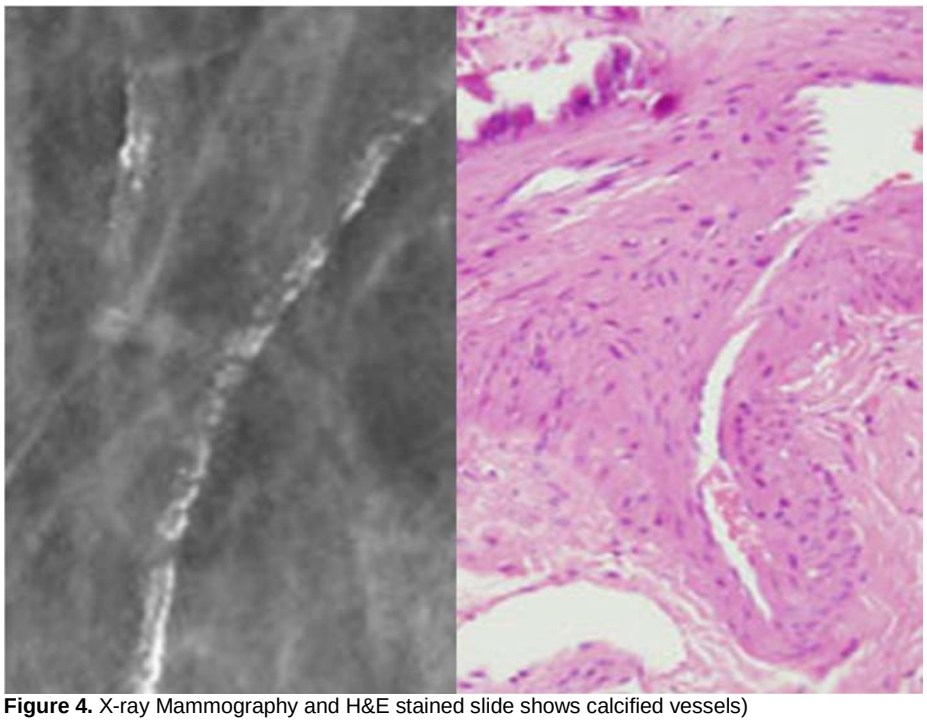

Figure 4. X-ray Mammography and H&E stained slide shows calcified vessels)

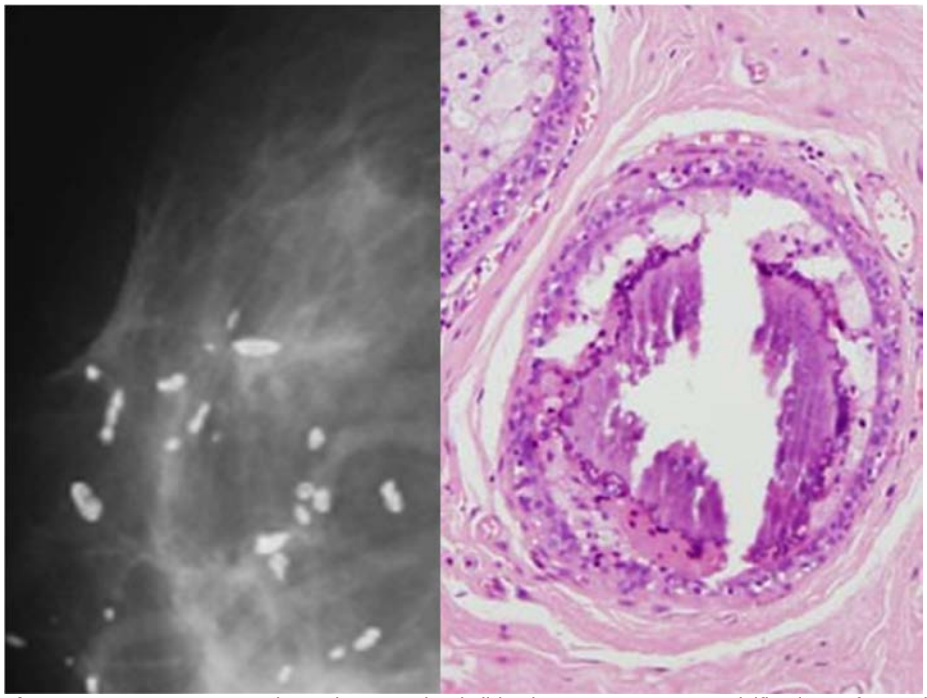

Figure 5. X-ray Mammography and H&E stained slide shows coarse macrocalcifications of ecstatic ducts)

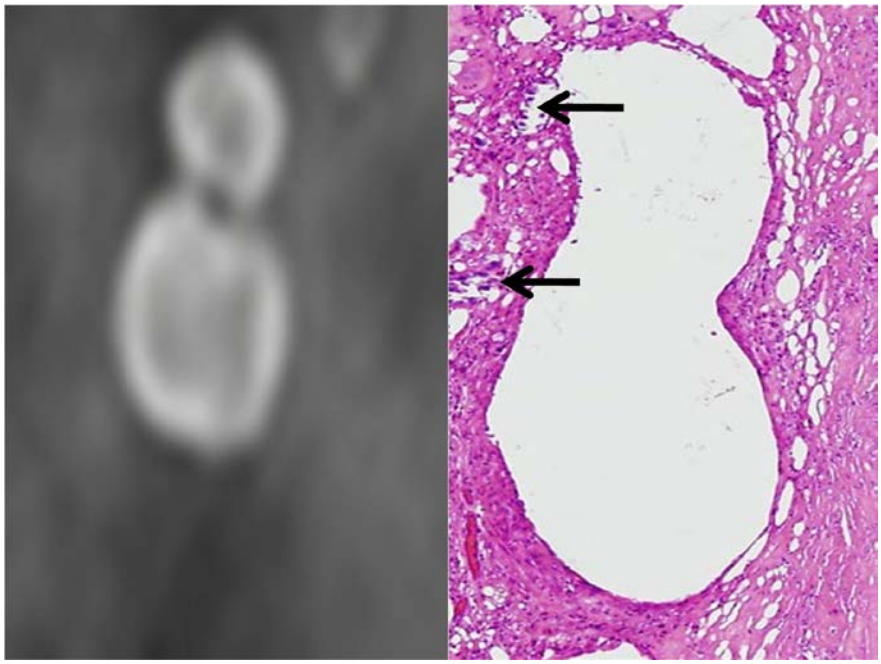

Figure 6. X-ray Mammography and H&E stained slide shows macrocalcifications with lucent centers in patient having fat necrosis in breast.

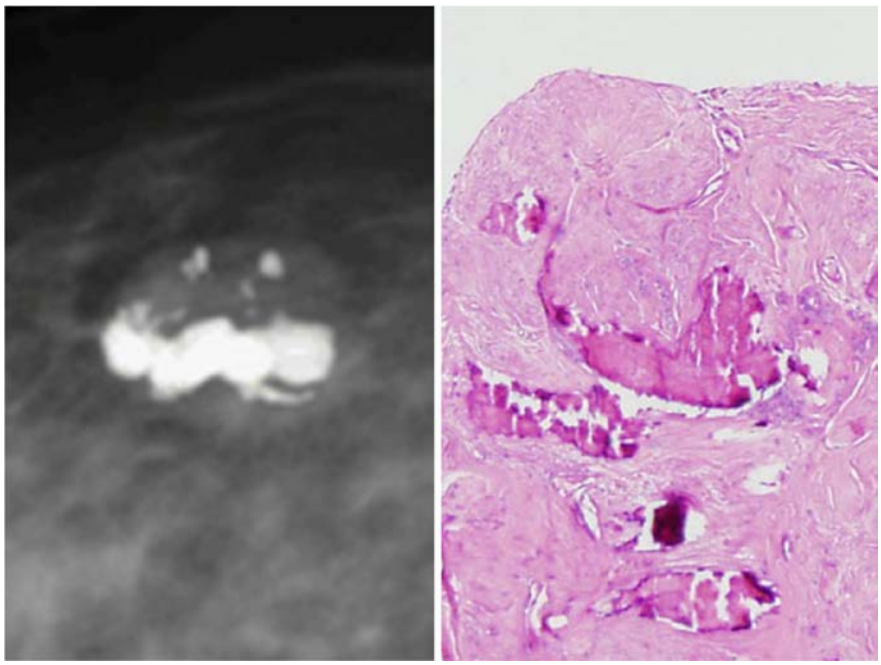

Figure 7. X-ray Mammography and H&E stained slide shows coarse macrocalcifications.

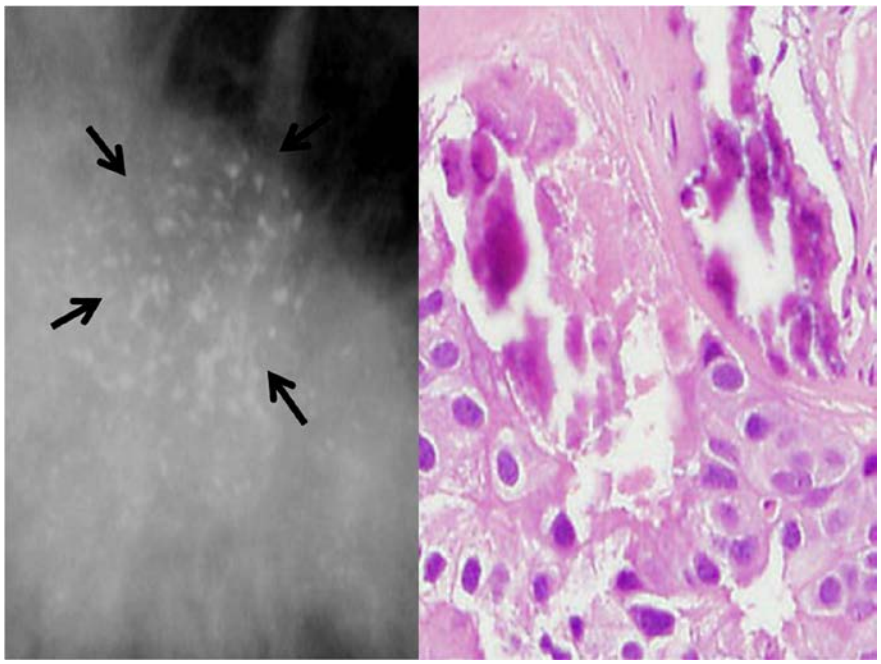

Figure 8. X-ray Mammography and H&E stained slide shows a group of microcalcifications in a diagnosed case of ductal carcinoma.

REFERENCES

1. Stephens TW, Whitman GJ, Stelling CB. Typical benign calcifications of the breast that do not require biopsy. The Radiologist. 2003;10:1-9.
2. Whitman GJ, Stephens TW, Hopkins K. Benign and malignant breast calcifications. Contemporary Diagnostic Radiology. 2002;25:1-6.
3. Borecky N, Rickard M. Preoperative diagnosis of carcinoma within fibroadenoma on screening mammograms. J Med Imaging Radiat Oncol. 2008;52:64-7.
4. Lehman CD, Rutter CM, Eby PR, White E, Buist DS, Taplin SH. Lesion and patient characteristics associated with malignancy after a probably benign finding on community practice mammography. AJR Am J Roentgenol. 2008;190:511-5.
5. Cardenosa G, Mendelson E, Bassett L, et al. Appropriate imaging work-up of breast microcalcifications. American College of Radiology. ACR Appropriateness Criteria. Radiology. 2000;215:973-80.
6. ACR. American College of Radiology: Illustrated Breast Imaging Reporting and Data System (BI-RADS). 3rd ed. Reston, VA: American College of Radiology. 1998.
7. D'Orsi CJ, Bassett LW, Berg WA, et al. Breast Imaging Reporting and Data System: ACR BI-RADS-Mammography (ed 4). 4th. Reston, Virginia: American College of Radiology. 2003.
8. D'Orsi CJ, Kopans DB. Mammographic feature analysis. Semin Roentgenol. 1993;28:204-30.
9. Bassett LW. Mammographic analysis of calcifications. Radiol Clin North Am. 1992;30:93-105.
10. Sickles EA. Breast calcifications: mammographic evaluation. Radiology. 1986;160:289-93.
11. Shin JH, Han BK, Ko EY, Choe YH, Nam SJ. Probably benign breast masses diagnosed by sonography: is there a difference in the cancer rate according to palpability? AJR Am J Roentgenol. 2009;192:187-91.
12. Tse, GM; Tan, PH; Pang, ALM; Tang, APY; Cheung, HS. Calcification in breast lesions: pathologists' perspective. Journal of Clinical Pathology. 2008;61:145-51.
13. Tse GM, Tan PH, Cheung HS, Chu WC, Lam WW. Intermediate to highly suspicious calcification in

breast lesions: a radio-pathologic correlation. Breast Cancer Res Treat. 2008;110:1-7.

14. Salgueira M, Martínez AI, Milán JA. Regression of vascular calcification in a patient treated with cinacalcet: a case report. Nefrologia. 2011;31:602-6.

15. Winchester DP, Jeske JM, Goldschmidt RA. The diagnosis and management of ductal carcinoma in-situ of the breast. CA Cancer J Clin. 2000;50:184-200.

16. D'Orsi CJ. Imaging for the diagnosis and management of ductal carcinoma in situ. J Natl Cancer Inst Monogr. 2010;2010:214-7.

17. Hofvind S, Iversen BF, Eriksen L, Styr BM, Kjellevold K, Kurz KD. Mammographic morphology and distribution of calcifications in ductal carcinoma in situ diagnosed in organized screening. Acta Radiol. 2011;52:481-7.

18. Winston JS, Yeh IT, Evers K, Friedman AK. Calcium oxalate is associated with benign breast tissue. Can we avoid biopsy? Am J Clin Pathol. 1993;100:488-92.

19. Gallagher R, Schafer G, Redick M, Inciradi M, Smith W, Fan F, Tawfik O. Microcalcifications of the breast: a mammographic-histologic correlation study using a newly designed Path/Rad Tissue Tray. Ann Diagn Pathol. 2012;16:196-201.

20. Tamaki K, Ishida T, Miyashita M, Amari M, Ohuchi N, Tamaki N, Sasano H.Correlation between mammographic findings and corresponding histopathology:potential predictors for biological characteristics of breast diseases. CancerSci. 2011;102:2179-85.

21. Zhang L, Liu Y, Song F, Zheng H, Hu L, Lu H, Liu P, Hao X, Zhang W, Chen K. Functional SNP in the microRNA-367 binding site in the 3'UTR of the calcium channel ryanodine receptor gene 3 (RYR3) affects breast cancer risk and calcification. Proc Natl Acad Sci U S A. 2011;108:13653-8.

22. Inoue K, Liu F, Hoppin J, Lunsford EP, Lackas C, Hesterman J, Lenkinski RE, Fujii H, Frangioni JV. High-resolution computed tomography of single breast cancer microcalcifications in vivo. Mol Imaging. 2011;10:295-304.

23. Jiang L, Ma T, Moran MS, Kong X, Li X, Haffty BG, Yang Q. Mammographic features are associated with clinicopathological characteristics in invasive breast cancer. Anticancer Res. 2011;31:2327-34.

24. Bennett RL, Evans AJ, Kutt E, Record C, Bobrow LG, Ellis IO, Hanby A, Moss SM. Pathological and mammographic prognostic factors for screen detected cancers in a multi-centre randomised, controlled trial of mammographic screening in women from age 40 to 48 years. Breast 2011;20:525-8.

Yazışma Adresi / Address for Correspondence:
Dr. Smita Balwant Sankaye
Rural Medical College, PIMS (DU)
Loni, Ta-Rahata, Ahmednagar Maharashtra
İNDİA
Email: smitasankaye@gmail.com

Geliş tarihi/Received on: 12.01.2014
Kabul tarihi/Accepted on:28.02.2014