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REVIEW

Intermediate to highly suspicious calcification in breast lesions: a radio-pathologic correlation

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Abstract Breast calcification is an important feature in the radiological assessment of breast lesions. There are well established diagnostic criteria basing on the morphology and distribution of the calcifications radiologically with recommendation protocols. Pathologically, calcifications in breast lesions are of dystrophic type, and may occur in either the secretory materials or necrotic debris, with inflammation and osteopontin being plausible mediators. Detection of calcium phosphate (hydroyapaptite) is considerably easier than calcium oxalate. Radiologically amorphous calcification represents a borderline type of calcification, and occurs in both benign and malignant (low grade) lesions, and warrants careful follow up and investigation. 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. Adequate sampling of calcification in the biopsy is crucial in the management of patients; in general, needle core biopsy or mammotome biopsy achieve satisfactory calcification retrieval. In a benign biopsy that fails to identify the calcifications visible in the mammography, further evaluation or cutting of the histologic block is recommended to minimize the potential of a false negative investigation.

Keywords Breast · Calcification · Cancer

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Introduction

In mammographic screening for breast cancer, calcification is one of the important features in the assessment and interpretation, and a good understanding of the morphologic features and the mechanism of calcifications and the potentials for misinterpretation is crucial for health care professionals involved in breast care. In fact, mammographically detected non palpable breast lesions often present as calcifications alone, calcifications with architectural distortion or calcifications associated with a mass [1].

One of the two most important roles of calcification detection in mammography is the identification of malignancy, many of which are carcinoma in situ, which has an excellent prognosis with appropriate therapy as it is pre invasive, and as such, does not possess metastatic potential. Interestingly the incidence of calcification in this group of lesion is more common in younger patients and in higher grade lesions [2–4].

The other important role is in the follow up of breast cancer patients having breast conservation therapy (BCT) as calcifications has been detected in 29–80% of recurrences, either as calcification alone or in association with other mammographic signs [4–7].

Radiological classification

The classification of breast calcification is based on the assessment of the morphology and the distribution.

The American College of Radiologist, in the Breast Imaging Reporting and Data System (BI-RADS), recommends that calcifications are to be reported according to the morphology and distribution [8–10].

The BI-RADS calcifications are listed as follows:

1. 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.
2. Intermediate concern calcifications: amorphous or indistinct calcifications or coarse heterogeneous calcifications.
3. Higher probability of malignancy: fine pleomorphic calcifications (granular) and fine linear, or fine linear branching (casting) calcifications.

In addition, the distribution of the calcifications is also noted, as diffuse or scattered, regional, grouped or clustered, linear, or segmental, with increasing risk of malignancy.

The overall assessment categorization is divided into:

Category 0—need additional imaging evaluation—assessment is incomplete, needing additional imaging evaluation—almost always used in the screening setting only
Category 1—negative—no abnormalities detected
Category 2—benign findings—some features worthy of description, but are confidently diagnosed as benign
Category 3—probably benign, short follow up interval suggested—the lesions have a high probability of being benign, but stability over time is preferably to be established
Category 4—suspicious abnormality—biopsy should be considered—although the lesions do not have the characteristic morphologies of breast cancer, they possess a definite probability of being malignant
Category 5—highly suggestive of malignancy, appropriate action should be taken.
Category 6—known biopsy proven malignancy—reserved for lesions with biopsy proof of malignancy.

Using a simplistic approach, calcifications that are large (greater than 1 mm), smooth, round, dense, scattered over a large area, bilateral or associated with some benign process are classified as benign. Clustered calcifications (at least 4–5 calcifications in 1 cm^3 area), in particular when they are pleomorphic or linear [11] are suggestive of malignancy. Stability over time should also be considered in the evaluation of calcifications. Static calcifications are considered benign, and new or increased calcifications may be viewed with suspicion. Calcifications that are neither clearly benign nor clearly malignant are considered indeterminate and must be treated as malignant until proven otherwise [1, 11–14].

Mechanism of calcification

Pathologic calcification is a common process in a wide variety of diseases, and it can be classified into dystrophic and metastatic calcification. Dystrophic calcification occurs in an abnormal local environment, without systemic calcium metabolic derangements; whereas metastatic calcification almost always occurs with hypercalcemia [15]. Dystrophic calcification may occur in areas of necrosis (particularly comedo necrosis of high grade ductal carcinoma in situ). The pathogenesis involves initiation and propagation, both of which may be intra- or extra- cellular, with crystalline calcium phosphate being the ultimate end product. Initiation in extracellular sites begins at membrane bound vesicles derived from degenerating cells, with concentration of calcium by virtue of its affinity for membrane phospholipids. Initiation in intracellular sites begins in the mitochondria of the dead or dying cells that have lost their ability to regulate intracellular calcium. Propagation of the calcification depends on the concentration of calcium, phosphate, presence of mineral inhibitors, and other proteins like osteopontin.

Metastatic calcification occurs with hypercalcemia due to other medical conditions that lead to increased parathyroid hormone production, increased destruction of bone, vitamin D related disorder or renal failure. This type of calcification can occur widely throughout the body, but the usual calcifications that are detected in the breast probably do not derive from this mechanism.

In breast tissue, there are two types of calcification molecules [16]. One is calcium oxalate, which is crystalline, amber, transparent, but birefringent on polarized light; the other is non crystalline, greywhite, non-birefringent, and contains calcium hydroxyapatite, which is a form of calcium phosphate. The former is usually not visible by H&E, and presents difficulty to be visualized without polarized light [17]. The Von Kossa stain has not been reported to be useful to detect calcium oxalate as well [18]. Interestingly this type of calcification is present mostly in benign lesions, particularly in those associated with apocrine changes [19].

In the breast, there are two types of calcification processes. The secretory type of calcification is related to secretion accumulation, hence it is likely to be found in

benign lesions, fibrocystic changes as well as low grade malignancies. The necrotic type of calcification is seen in comedo necrosis, and this is caused by the rapidly proliferating tumor cells outstripping the vascular supply, resulting in tumor cell death, particularly in the center of the ductal lumen. Apparently the cell death and the subsequent increased acidosis in the microenviron results in denaturation of structural and enzymatic proteins, with blocking of the cellular proteolysis and the preservation of the structural features, resulting in the formation of necrotic debris which subsequently calcifies with retention of the structure of the large ductal system, thus forming the typical linear, branching and casting type of calcification.

Osteopontin appears to be a crucial mediator involved in the process of calcification. This mediator was found in the histiocytes around the lesional epithelial breast tissue [20, 21], but at much lower level in tumor cells [21, 22]. There is evidence that the same mediator of ostropontin is involved in the 'secretory' and the 'necrotic' type of calcification. It has been found that high level of osteopontin is present in milk, and it is very likely that in fibrocystic changes and those with secretory type calcification, ostropontin level is increased within the lumen [23, 24]. The observation that the osteopontin in the milk may actually inhibit crystal growth [25, 26] may account for the granular appearance of this type of calcification. In the scenario of high grade tumor, osteopontin expression may actually represent part of the inflammatory response process to cellular damage. As observed before, most of the osteopontin is probably synthesized by macrophages likely recruited as part of the necrosis induced inflammatory response [27].

Specific types of calcifications and the pathological correlation

Amorphous calcification

While the typical benign or malignant type calcification morphologies have good positive and negative predictive values, the amorphous type calcifications have been considered of intermediate concern. The specific description is 'sufficiently small or hazy that a small specific morphological classification cannot be made' [10]. With the increased sensitivity of mammography, this type of calcification is more readily detected and submitted for pathologic evaluation [28], and it was reported that 60% of these amorphous calcifications were benign, being found in fibrocystic changes, fibrosis, sclerosing adenosis, usual hyperplasia, fibroadenomas, benign stromal calcification, secretory change, duct papilloma and apocrine metaplasia. Among these, the first three entities account for more than 86% of all the benign lesions. About 20% were malignant, with invasive carcinoma accounting for a minority (10%) of all malignant lesions, and ductal carcinoma in situ accounting for the remaining majority (90%). Even the invasive lesions were small, all of which were less than 5 mm. For the ductal carcinoma in situ, most of the malignancies with amorphous calcifications were of low nuclear grade (60% of all ductal carcinoma in situ), with intermediate and high nuclear grade lesions accounting for 28% and 12% respectively of all ductal carcinoma in situ. Interestingly, in 6% of the cases, the calcifications were found in the benign tissue adjacent to the ductal carcinoma in situ, but not within the lesion. Atypical lesions including atypical duct hyperplasia, atypical lobular hyperplasia and lobular carcinoma in situ accounted for another 20% of the series. Of interest is that most calcifications of the ADH were lesional, whereas those for ALH and LCIS were mostly in the adjacent benign breast tissue rather than within the lesion.

To put this into perspective, in the same series and among all the lesions that showed calcification, about 33, 84 and 50% respectively of breast ductal carcinoma (invasive and in situ), atypical duct hyperplasia and lobular neoplasia (ALH and LCIS) with calcification showed amorphous type calcification.

It thus appears that a significant proportion of amorphous calcification is malignant, ranging from 20% to 26% [8, 28]. The distribution of the calcifications is also important. It has been reported that even for amorphous calcifications, those in segmental or linear distributions had higher chances of being malignant (about 40–70%) compared to clustered distribution (about 17–36%) [8, 28]. Pathologically, the calcification is more likely to be of secretory type, which can occur in both benign lesions as well as in low grade malignancy devoid of necrosis. The distribution of the calcification is also a reflection of the pathology. In malignant lesions, there is more likely to be involvement of the single ductal system, with higher density of the malignancy associated amorphous calcification present within a linear or ductal distribution, whereas in benign lesions, the involvement tends to be more diffuse, hence the resulting calcification may be more clustered and transgressed the boundaries of the segments or ducts.

Linear or branching calcification

Linear or branching calcifications are usually associated with high grade, poorly differentiated carcinomas with comedo type necrosis, with some overlap [29]. This phenomenon is valid for both in situ and invasive lesions [30–35]. For the prognostication of this group of malignancy, particularly when the tumor is small in size so that they are only screen detected (less than 15 mm), it has been

suggested that histologic grade and stage alone may not be reliable indicators for prognosis [36, 37], and the presence of comedo necrosis may be an important prognostic factor for these small, tumors [35, 37, 38], albeit this group in general tends to behave better than larger tumors of the same grade. It has been demonstrated that linear calcification was associated with worse outcome (lower 5 year survival) [35], risk of recurrence [35], residual microscopic disease [39], extensive in situ component [39], but not lymphovascular permeation [39]. Another recent study involving a large series of patients however failed to demonstrate any association between casting calcification and survival, although the casting calcification was closely related to the histologic grade [40]. The pathological correlation is easy to understand, as the presence of linear calcification denotes the presence of comedo necrosis, which occurs within the geographic location of the ducts with dystrophic calcification that one tends to see in high grade lesions, particularly in DCIS. This would imply high grade and probably high chance of residual disease after lumpectomy by virtue of the significant in situ component. (Figs. 1, 2)

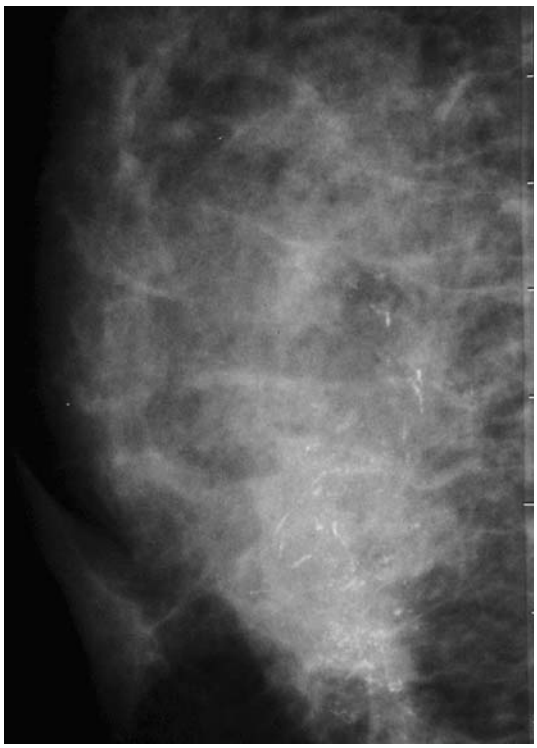

Fig. 1 CC view mammography showing rod shaped, casting calcification in the right breast

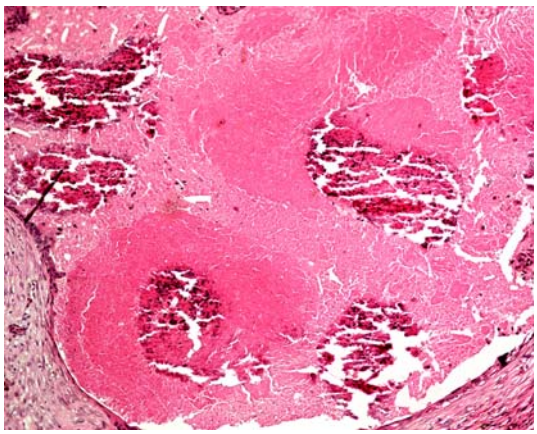

Fig. 2 Corresponding histology showing ductal carcinoma in situ with distended ductal space with necrosis and foci of calcification in the center

Distribution of calcification and correlation with pathological findings

Clustering of calcifications

There is an increased risk of malignancy associated with increased number of calcifications [41, 42]. The definition of clustered calcification is taken as more than 5 microcalcifications in an area of 1 cm^2, or an area of 0.5 cm × 0.5 cm or in the volume of 1 cc [42–44].There is however considerable overlap between benign and malignant lesions with clustered calcifications, making this morphological description somewhat non discriminatory (Figs. 3, 4). To enhance the discriminatory power of clustered calcification, many authors have reported that the number of calcifications within an area is an important parameter of clustered calcifications. When the number of calcification is low (less than 5 per 0.25 cm^2 [43], or less than five per cluster [44], or when the calcifications are present in a loose cluster [45]), the lesions are very unlikely to be malignant. In addition, other associated parameters have been reported to be important in predicting malignancy, and these include pleomorphism of the calcification, architectural distortion, associated mass and associated density. Interestingly clustering alone is not associated with malignancy [44]. It would thus appear that the clustered calcification by itself may not be a good malignant indicator, but when there is associated density or mass, increased number of calcification and pleomorphic morphology may point strongly to a malignant lesion. Hence the interpretation of clustered calcification has to be in conjunction with these other parameters. Pathologically these small sized calcifications are likely to be of secretory type rather than the comedo (necrotic) types, thus explaining the fact that both benign and malignant lesions may show this type of clustered calcification. The type of malignancy is expected to be low grade without necrosis, and the higher number of calcification may be caused by

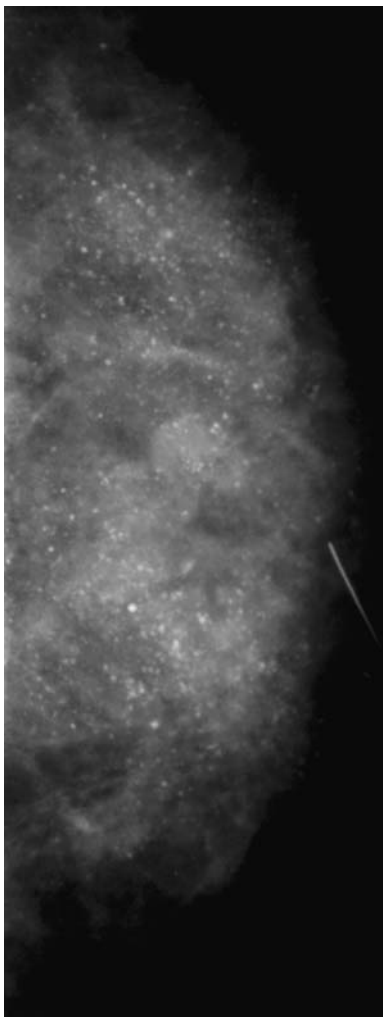

Fig. 3 CC view mammography showing punctuate irregular calcification over the entire left breast

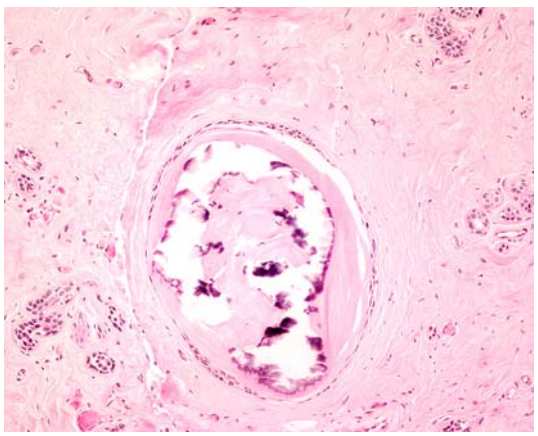

Fig. 4 Corresponding histology showing fibrocystic changes with calclfication present within dilated ductal lumen, probably from secretory material

the higher cellularity in the malignant than benign lesions. The associated architectural distortion as well as tissue mass on mammography may indicate the presence of tumor desmoplasia, which is a tissue fibrotic reaction to tumor invasive, resulting in contraction of the area forming a stellate or crab like pattern with dense tissue pattern or architectural distortion, as the newly formed fibrotic tissue may possess mild contractile property.

Calcification and biopsy

One of the main issues of radiologic pathologic correlation in breast calcification is the correct and adequate sampling of the calcifications in question and the subsequent pathologic diagnosis. The sampling methods include the widely practiced stereotactic needle core biopsy and mammotome, with the latter usually giving larger core size samples. In general, the retrieval of calcifications at stereotactic needle core biopsy is satisfactory, ranging from about 77% to almost 100%, with a mean value of about 86% [46–49]. The detection rate depends on many factors, and an adequate sample is important. It has been recommended that at least 3 cores with 5 or more flecks of calcium is essential to ensure high pre-operative diagnostic rate for malignant calcifications [50], and mammotome biopsy, which tends to obtain more tissue for histology, has a lower missing rate for calcification [48, 49]. Another factor that contributes to the negative detection rate is the nature of the calcification. Calcium hydroxyapatate, which is a type of calcium phosphate, tends to be visible on routine histologic sections, whereas the other major type, calcium oxalate, is not visible at routine histologic staining. If calcification is present in the specimen radiograph but not in the histology slide, this could be caused by either loss of calcium during processing [51, 52], or the tissue has not been completely sectioned. If calcification is not present in the specimen radiograph but is identified in the histologic section, then the histologic calcification does not represent the mammographic calcification as the former is much smaller and would not have been resolved in the mammography. What is then the significance of identification of calcification in the biopsy? There is no relevance if the biopsy shows malignancy. It is in the atypical or benign biopsies that one has to be very careful in correlating the histologic calcification with the mammographic calcification. Correlation with the size of the calcification may be helpful, bearing in mind that calcifications less than 100 microns may not be significant as these are not radiologically detectable [46]. Most malignant calcifications range from 100 to 300 microns in size [53]. If calcification is present in the specimen radiographs but not in the initial histology sections, and the initial histologic diagnosis is non malignant,

it is prudent to order deeper sections to search for the calcifications, and a reduction of false negative rate of up to 6% has been reported [46] by this procedure.

Conclusion

Assessment of calcification in breast lesions requires understanding the radiologic observation, terminology and the underlying pathologic mechanisms. While the calcifications associated with malignancy have a typical appearance due to necrosis, some low grade malignancies and benign lesions show overlapping calcification patterns. Particular attention has to be paid in the management and investigation of lesions characterized as amorphous calcification and clustered calcification, and in lesions showing discrepancy in calcification detection between mammography and biopsy.

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