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ORIGINAL RESEARCH

Breast Suspicious Microcalcifications on Contrast-Enhanced Mammograms: Practice and Reflection

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Purpose: To evaluate the use of contrast enhanced mammography (CEM) in suspicious microcalcifications and to discuss strategies to cope with its diagnostic limitations.

Methods: We retrospectively evaluated patients with suspicious calcifications who underwent CEM at our institution. We collected and analyzed morphological findings, enhancement patterns and pathological findings of suspicious microcalcifications on CEM. A small proportion of these cases underwent dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). The enhancement patterns of CEM in this study were classified into three categories: enhancement, no enhancement, and indeterminate. CEM imaging was independently analyzed by two breast imaging specialists.

Results: A total of 44 patients with 46 lesions were collected from January 2022 to July 2024. Overall, 20 cases (43.5%) microcalcifications showed enhancement on CEM; 23 (50.0%) showed no enhancement; and 3 (6.5%) were indeterminate. Of the 20 enhancement cases, mass enhancement was seen in 9 (45%), and non-mass enhancement (NME) in 11 (55%). DCE-MRI was performed in 13 cases. One case of invasive ductal carcinoma (IDC) showed enhancement on MRI but was indeterminate on CEM due to the masking effect of background parenchymal enhancement (BPE), and one case of ductal carcinoma in situ (DCIS) lacked enhancement on CEM but had significant enhancement on MRI.

Conclusion: CEM provides additional information on the enhancement associated with breast suspicious microcalcifications. It is not perfect for diagnosis and strategies are needed to cope with its limitations.

Keywords: microcalcifications, contrast-enhanced, mammography, diagnostic imaging, breast

Introduction

Breast calcification continues to be a huge challenge in terms of diagnosis and management.[1–3] According to the BI-RADS 5th edition lexicon, suspicious calcifications are classified into two categories: category 4B (amorphous, coarse heterogeneous and fine polymorphous) and category 4C (fine linear/fine linear branching calcifications).[4] BI-RADS morphology and distribution descriptors help assess the malignancy risk of microcalcifications detected by digital mammography (DM). However, the positive predictive value (PPV) of microcalcifications assessed by mammography varies widely and is usually less than 30%.[5]

Dynamic contrast-enhanced breast magnetic resonance imaging (DCE-MRI) is the most sensitive imaging modality currently available.[6] However, the disadvantage of MRI is the inadequate display of microcalcifications. Contrast-enhanced mammography (CEM) is a relatively new breast imaging modality that obtains recombined images (RC) representing the relative distribution of iodine in the breast.[7] Theoretically, CEM can more accurately assess breast calcifications because it combines the visibility of calcifications with vascular information in recombined image (RC).[8]

Previous studies have classified the enhancement pattern of suspicious microcalcification sites into two categories: enhancement and non-enhancement.[9–12] However, CEM is a planar imaging exam, and consequently small abnormalities

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may blend with background parenchymal enhancement (BPE) when it is moderate or marked. BPE refers to the uptake of contrast by normal fibroglandular tissue and can be observed on magnetic resonance imaging (MRI) and CEM.[13] Due to the overlap of fibroglandular tissue and overlying BPE, BPE may have a relatively larger impact on CEM interpretation than MRI.[14]

Therefore, to categorize them in more detail, this study divides the enhancement patterns into three categories: enhancement, no enhancement, and indeterminate, which may be more in line with practical applications.

This study aimed to evaluate the use of CEM in suspicious microcalcifications and to discuss strategies to cope with its diagnostic limitations.

Methods

This study was approved by the Ethics Committee of Huangpu Branch, Shanghai Ninth People's Hospital, Shanghai Jiaotong University School of Medicine. Informed consent was waived because of the retrospective design of the study. The anonymity and confidentiality of the participants were guaranteed. We certify that this study was conducted in accordance with the Declaration of Helsinki.

Inclusion criteria were patients with suspicious calcifications on original mammograms (reported as BI-RADS 4B, 4C) and no related mass lesions on physical examination or breast ultrasound. Pathology results, either by wire-guided biopsy or by operation, could be obtained from medical records in our hospital.

Exclusion criteria were impaired renal function or a history of contrast allergy.

CEM Examination

CEM examinations were performed using the Senographe Pristina mammography system (GE Healthcare). Examination was standardized and performed with intermittent exposure to low and high energy during a single breast-compressed position after the injection of nonionic contrast medium (iodixanol 350 mg I/mL, Yangzijiang Pharmaceutical Co. Ltd) at a rate of 3 mL/s for a total dose of 1.5 mL/kg body weight.

Dual-energy exposures were performed in bilateral craniocaudal (CC) and mediolateral oblique (MLO) views. Each view contained a low-energy image (LE) and a recombined image (RC). The RC was obtained from the subtraction of low- and high-energy images.

CEM were analyzed by two radiologists with 15 years and 20 years' experience. The CEM findings were reviewed according to the newly published BI-RADS CEM (2022). BI-RADS final categorization of each lesion was performed by one of the radiologists.

MRI Examination

Out of the 46 cases included in our study, 13 of them were imaged using the 3.0 T MRI scanner (uMR780, China) with a dedicated breast coil was used for breast MR imaging. In our institution, 6 dynamic sequences are performed: 1 basal pre-contrast acquisition followed by 5 continuous acquisitions after contrast agent administration (0.1 mmol/kg at a flow rate of 2 mL/s) injected via an automated injector, followed by a saline flush (20 mL at the same flow rate).

Of all lesions, pathological results were available. Wire-localized excision or biopsy of suspicious lesions was performed for analysis of pathological diagnosis. Surgical specimens and biopsies were evaluated according to current national guidelines.

Discrete variables are expressed as counts and percentages, whereas continuous variables are reported mean ± standard deviation (SD) or as median and interquartile range.

Results

A total of 44 patients with 46 lesions were collected with CEM examination from January 2022 to July 2024. The mean age of the patients was 51 years ± 12 (standard deviation) (range, 26–70 years).

The most common breast density was heterogeneously dense (50.0%, Table 1), and the most prevalent calcification type was pleomorphic calcification (37.0%, Table 1), followed by amorphous calcification (32.6%). BPE were prevalent in mild (39.1%) and moderate (28.3%).

Table 1 Features of the 46 Lesions (Suspicious Calcifications)

Variable	Cases (Percentages)
Breast Density	
Almost entirely fatty	2(4.3%)
Scattered fibroglandular	7(15.2%)
Heterogeneously dense	23(50%)
Extremely dense	14(30.4%)
BPE level	
Minimal	9(19.6%)
Mild	18(39.1%)
Moderate	13(28.3%)
Marked	6(13.0%)
Enhancement presence	
YES	20(43.4%)
NO	23(50.0%)
Indeterminate	3(6.5%)
Enhancement type	
Mass	9(45%)
Non-mass enhancement	11(55%)
Calcification morphology	
Amorphous	15(32.6%)
Coarse heterogeneous	6(13.0%)
Fine pleomorphic	17(37.0%)
Fine linear/ fine linear branching	8(17.4%)

Abbreviations: BPE, background parenchymal enhancement; NME, non-mass enhancement.

Table 2 Distribution of Enhancement Patterns, Pathological Diagnosis, and BI-RADS Category

Types		Benign (n=24)	DCIS (n=17)	Invasive Carcinoma (n=5)
BI-RADS category	BI-RADS4B(n=38)	22(91.7%)	12(70.6%)	4(80.0%)
	BI-RADS4C(n=8)	2(8.3%)	5(29.4%)	1(20.0%)
Enhancement presence	YES (n=20)	2(8.3%)	14(82.3%)	4(80.0%)
	NO (n=23)	20(83.3%)	3(17.6%)	0
	Indeterminate(n=3)	2(8.3%)	0	1(20.0%)

Abbreviations: DCIS, ductal carcinoma in situ; BI-RADS, Breast Imaging Reporting and Data System.

20 cases (43.5%) microcalcifications revealed enhancement on RC, 23 cases (50.0%) showed no enhancement, 3 cases (6.5%) were indeterminate due to the masking effect of BPE (Table 2). Of the 20 enhancement cases, mass enhancement was seen in 9 (45%), and non-mass enhancement (NME) in 11 (55%). There were 38 cases of BI-RADS 4B and 8 cases of BI-RADS 4C. The distribution of enhancement patterns, pathological diagnoses and BI-RADS categories is shown in Table 2.

Of the 20 cases with enhancement of suspicious microcalcifications, 18 were malignant (Figure 1, Table 3) and 2 were benign. Of the 23 cases with no enhancement, 3 were malignant and 20 were benign (Figure 2, Table 3).

Out of the 46 cases included in our study, 13 of them underwent DCE-MRI, of which 8 showed enhancement and 5 did not (Table 3). One case of invasive ductal carcinoma (IDC) showed enhancement on MRI but was indeterminate on

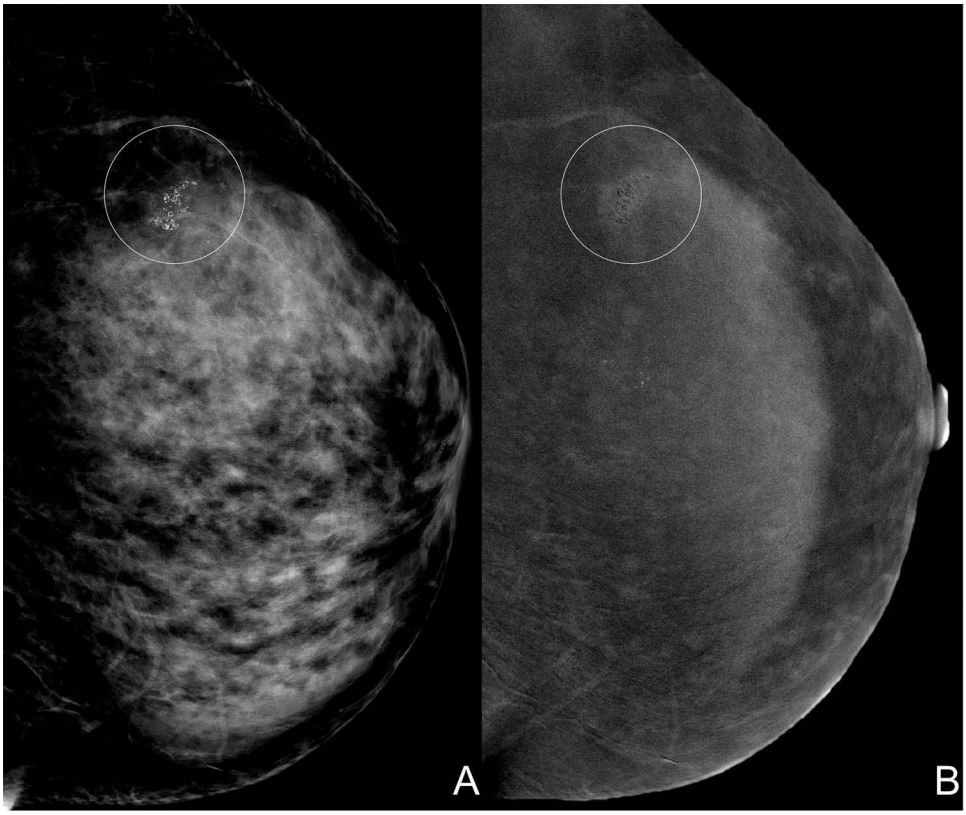

Figure 1 A 36-year-old female. (**A**)Mediolateral oblique (MLO) view of low energy image (LE) shows heterogeneously dense breast, and fine pleomorphic calcification (BI-RADS 4B) in the upper quadrant of the left breast (white circle). (**B**) Recombined image (RC) shows a moderate level of background parenchymal enhancement (BPE), and mass enhancement at the area of the calcification (white circle). The histological diagnosis was ductal carcinoma in situ.

CEM due to the masking effect of BPE (Figure 3), and one case of ductal carcinoma in situ (DCIS) lacked enhancement on CEM but had significant enhancement on MRI (Figure 4). The remaining 11 lesions (84.6%) had consistent CEM and MRI performance.

72.2% (N=17) of the malignant lesions were categorized as DCIS, and 27.7% (N=5) were invasive carcinoma. The benign lesions that enhanced on CEM included one case of sclerosing adenopathy, one case of atypical ductal hyperplasia (ADH). 22 benign lesions that did not enhance, including proliferative and nonproliferative disease.

Table 3 Distribution of Enhancement Types Observed by CEM and MRI

	Benign n (%)	**Malignant n (%)**	**Total n (%)**
CEM			
Mass	1(4.2%)	8(36.3%)	9(19.6%)
Non-mass enhancement	1(4.2%)	10(45.5%)	11(23.9%)
No enhancement	20(83.3%)	3(13.6%)	23(50.0%)
Indeterminate	2(8.3%)	1(4.5%)	3(6.5%)
MRI			
Mass	0	5(71.4%)	5(38.4%)
Non-mass enhancement	1(16.7%)	2(28.6%)	3(23.1%)
No enhancement	5(83.3%)	0	5(38.4%)

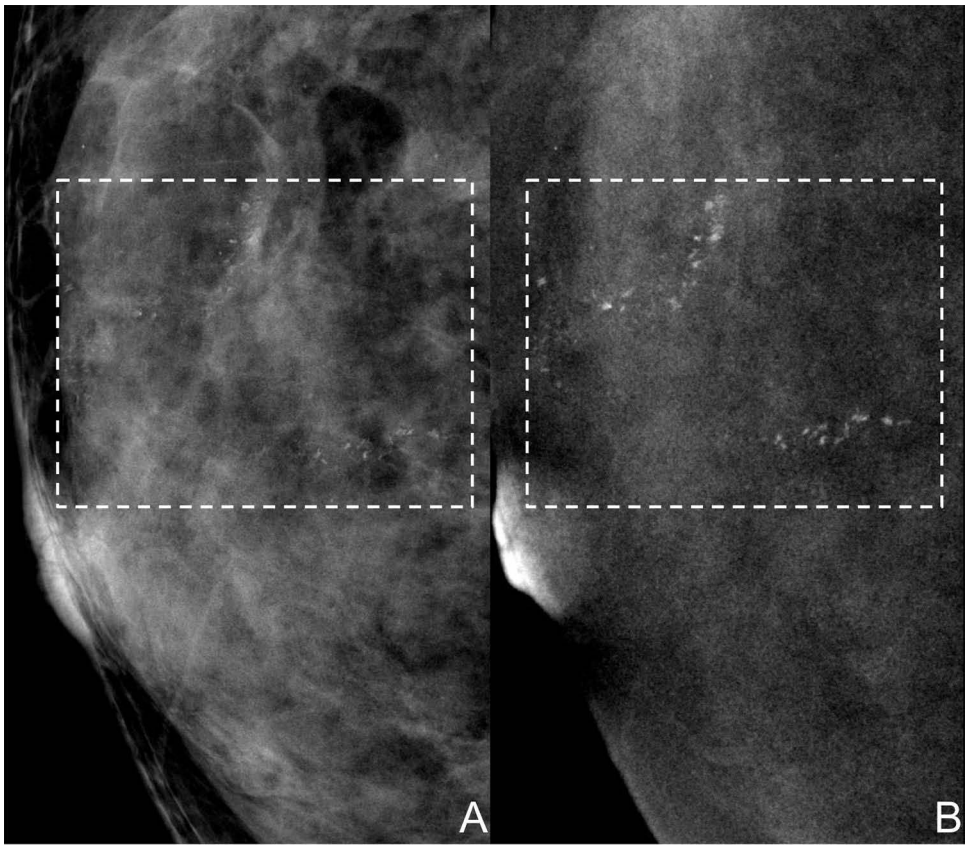

Figure 2 A 26-year-old female. (**A**)Mediolateral oblique (MLO) view of low energy image (LE) shows heterogeneously dense breast, fine linear calcifications (BI-RADS 4C) in the upper quadrant of the right breast (white rectangle). (**B**) Recombined image (RC) shows a mild level of background parenchymal enhancement (BPE), and no enhancement at the area of calcification (white rectangle). The histological diagnosis was intraductal calcification.

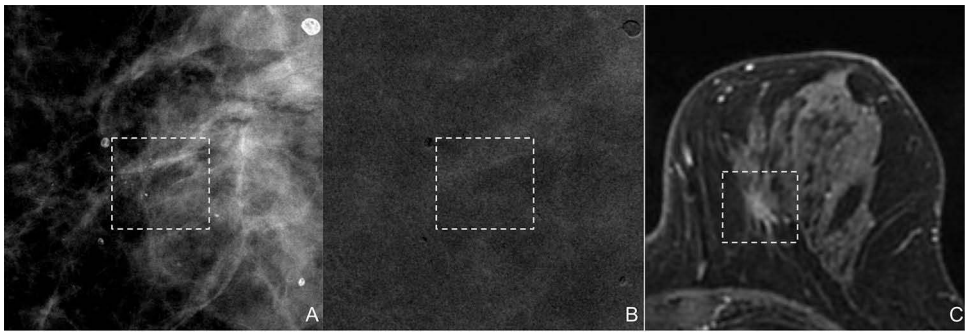

Figure 3 A 69-year-old female. (**A**) Craniocaudal (CC) view of low energy image (LE) shows heterogeneously dense breast, and amorphous calcifications (BI-RADS 4B) in the medial quadrant of the left breast (white rectangle). (**B**) Recombined image (RC) shows a moderate level of background parenchymal enhancement (BPE), the presence or absence of enhancement at the site of calcification is uncertain (white rectangle). (**C**) Magnetic resonance imaging (MRI) shows non-mass enhancement in the same position of the left breast (white rectangle). The histological diagnosis was invasive ductal carcinoma.

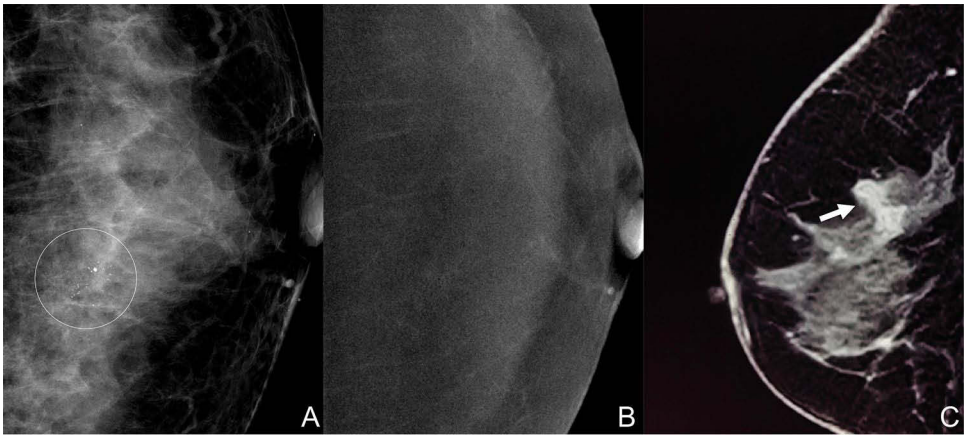

Figure 4 A 63-year-old female. (**A**) Craniocaudal (CC) view of low energy image (LE) shows heterogeneously dense breast, and amorphous calcifications (BI-RADS 4B) in the medial quadrant of the left breast (white circle). (**B**) Recombined image (RC) shows a mild level of background parenchymal enhancement (BPE) and lack of enhancement at the area of the calcification. (**C**) Sagittal magnetic resonance imaging (MRI) shows mass enhancement in the same position of the left breast (arrow). The histological diagnosis was ductal carcinoma in situ.

Discussion

Early detection of breast cancer depends to a large extent on the correct interpretation of suspicious microcalcifications. Particularly, most DCIS cases are identified on mammography, and 90% of DCIS are associated with calcification.[15]

As in previous studies, the presence or absence of enhancement on RC imaging cannot be used to classify calcifications as benign or malignant[9,10] but malignant lesions are more often associated with enhancement than benign lesions,[11] which is consistent with our findings. For this reason, any suspicious calcifications should be examined based on their appearance on LE, conventional mammography.

In our study, there were three cases in which enhancement could not be determined on CEM due to the masking effect of the BPE, and one IDC was confirmed by MRI to have enhancement at the corresponding site. Since DCE-MRI is the most sensitive imaging modality currently available, it can be inferred that BPE is related to false negative CEM exams. In addition, BPE may have a greater impact on CEM than MRI, because additional information is not available for CEM.[14]

Current research findings on CEM are discrepant. Depretto et al reported that the total of DCIS G1 lesions 100% (N=6) lacked enhancement, while 100% of invasive carcinomas (N=16) demonstrated enhancement.[9,10] Houben et al reported that the only low-grade DCIS showed enhancement, 11% of the high-grade DCIS did not show enhancement.[8] However, in our small series, 4 cases invasive carcinomas and 76.4% of DCIS (N=14) showed enhancement; 3 DCIS showed no enhancement, and 1 IDC was uncertain due to BPE interference. Further studies with large samples are needed regarding inconsistencies in CEM results.

To the best of our knowledge, comparative CEM and MRI studies of breast suspicious microcalcifications are currently rare. According to a report specializing in DCIS, all DCIS lesions enhance on MRI, while on CEM, 5 calcified DCIS lesions were unenhanced in CEM,[16] which also suggests that calcified DCIS that does not enhance on CEM may show enhancement on MRI. The demonstration of the presence or lack of enhancement of microcalcifications by MRI and CEM may be inconsistent. In our study, one case of DCIS showed enhancement on MRI but not on RC, which led to the speculation that MRI may be superior to CEM in terms of haemodynamics of the lesion, and that the false-negative findings of CEM may be related to the lack of enhancement of the lesion. Due to the small number of cases undergoing MRI in this study, there is a lack of data from a large sample to draw definitive conclusions.

Limitations of CEM are associated with false-positive and false-negative results. Benign lesions with blood vessels, infections or inflammation, benign skin lesions, and imaging artefacts may cause false-positive. False negatives may be caused by inadequate or complete incorporation of the lesion, the masking effect of BPE, and the absence of contrast enhancement in malignant tumours.[7] In addition, some lesion features on the subtracted CEM image are compromised due to the lower contrast resolution, including poorly defined borders.[17]

Some strategies are needed to cope with these limitations. For BPE, it is currently believed to be related to endogenous hormonal status and fluctuates with the menstrual cycle.[18] It was reported that premenopausal patients

with regular menstrual cycles have the lowest BPE levels on days 8–14 of the menstrual cycle on CEM.[14] This association can inform decisions about scheduling CEM examinations based on the timing of the menstrual cycle.

Lack of enhancement on RC images is not a reliable indicator to exclude malignancy. For this reason, both the morphology and enhancement features of suspicious microcalcifications are important for diagnosis. In addition, any enhancement that is not considered to be BPE should be fully evaluated, even if the level of enhancement is low according to newly published BI-RADS CEM (2022).

Our study has several limitations. The number of patients was limited, and the number of cases with histological diagnoses might have selective bias. This is a preliminary analysis of the comparison of CEM and MRI for suspicious microcalcifications, and a large sample study is needed for further evaluation.

In conclusion, CEM provides additional information on the enhancement associated with breast microcalcifications. However, data on CEM is still limited and performance is consequently uncertain. It is not perfect for diagnosis and strategies are needed to cope with its limitations.

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Disclosure

The author reports no conflicts of interest in this work.

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