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ORIGINAL ARTICLE

Grouped Amorphous Microcalcifications on Mammography: A Single-Centre 8-Year Retrospective Cohort Study on an Asian Population

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ABSTRACT

Introduction: *Grouped amorphous microcalcifications on mammography are classified as BI-RADS (Breast Imaging Reporting and Data System) category 4B. While recent international studies support a lower subcategory (4A), we sought to measure the malignancy rate of grouped amorphous microcalcifications classified as BI-RADS category 4A or above in the Asian population.*

Methods: *All cases at our hospital with any kind of suspicious microcalcifications underwent either stereotactic-guided vacuum-assisted biopsy or excisional biopsy with stereotactic localisation from 2013 to 2020 were retrieved. Cases with grouped amorphous microcalcifications as the most suspicious morphology on magnified views were selected. Only cases with at least 2 years of follow-up were included. Final histological diagnosis was based on the highest grade of tissue diagnosis at biopsy or excision.*

Results: *Among 333 biopsied cases, 121 were grouped amorphous microcalcifications. The majority of patients (92.5%) were ethnic Chinese while the rest (7.5%) were Pacific Islanders. A total of 4.1% (n = 5) had malignant final pathology, with four ductal carcinomas in situ (DCIS) and one invasive ductal carcinoma. A total of 9.1% (n = 11) had high-risk pathology (all atypical ductal hyperplasia). In two cases, the microcalcifications were located adjacent to surgical scars, with one diagnosed as DCIS.*

Conclusion: *The malignancy rate of grouped amorphous microcalcifications in our study is in line with recent studies, providing support for classifying a BI-RADS category 4A for these calcifications. The majority of the malignant lesions came back as DCIS, which carries promising post-treatment survival rates. Histological diagnosis remains indicated for grouped amorphous microcalcifications, yet more nuanced management plans may be employed in the future.*

Key Words: *Breast; Calcinosis; Neoplasms*

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Ethics Approval: The research was approved by the Hong Kong East Cluster Research Ethics Committee of Hospital Authority, Hong Kong (Ref No.: HKECREC-2022-062). Informed patient consent was waived by the Committee due to the retrospective nature of the research.

中文摘要

乳房X光檢查中的聚集無定形微鈣化：亞洲人群的單中心8年回顧性隊列研究

馮喬政、黎爾德、黃可澄、巫冠文、錢凱、黃慧中

引言：乳房X光檢查中的聚集無定形微鈣化歸類為 BI-RADS（乳房影像報告和數據系統）類別 4B。雖然最近的國際研究支持更低的子類別（4A），但我們嘗試評估亞洲人群中分類為BI-RADS 4A類或以上的聚集無定形微鈣化的惡性率。

方法：我們檢索於2013至2020年期間在本院接受立體定位真空輔助活檢或立體定位切除活檢的所有疑似微鈣化病例，並選擇放大視圖中最可疑的形態學為聚集無定形微鈣化的病例。我們僅納入至少追蹤兩年的病例。最終的組織學診斷是基於活檢或切除時組織學診斷的最高等級。

結果：333例活檢中，121例為無定形微鈣化。大多數患者（92.5%）是華裔，其餘患者（7.5%）是太平洋島民。總共4.1%（n = 5）最終病理為惡性，其中4例為導管原位癌，1例為浸潤性乳管癌。總共9.1%（n = 11）有高風險病理（皆為非典型導管增生）。2例的微鈣化位於手術疤痕附近，其中1例被診斷為導管原位癌。

結論：本研究中分組的無定形微鈣化的惡性率與最近的研究一致，為這些鈣化的BI-RADS 4A 類分類提供了支持。大多數惡性病變以導管原位癌的形式復發，治療後的存活率良好。組織學診斷仍適用於聚集無定形微鈣化，但未來可能會採用更細緻的處理計劃。

INTRODUCTION

Amorphous morphology is categorised as 4B in the fifth edition of BI-RADS (Breast Imaging Reporting and Data System) of the American College of Radiology (ACR), with a positive predictive value of malignancy of approximately 20% based on older case series.[1] Recent retrospective studies, including mostly Western populations, have reported a malignancy rate of ≤10% for grouped distribution, which may suggest a more nuanced treatment approach.[2,3]

Studies targeting grouped microcalcifications in the Asian population are lacking. A relatively representative study including 216 subjects by Iwase et al[4] reported a malignancy rate of 2.8% in the Japanese population. The objective of our study was to report the malignancy rate of grouped amorphous microcalcifications in the Asian population.

METHODS

Mammographically detected microcalcifications classified as BI-RADS category ≥4A are routinely scheduled for biopsy in our centre at Pamela Youde Nethersole Eastern Hospital in Hong Kong. We retrieved all such cases that underwent either stereotactic-guided vacuum-assisted biopsy or excisional biopsy with stereotactic-guided localisation from 2013 to 2020 in our centre from the electronic patient record.

Preprocedural mammograms were reviewed independently by two breast radiologists (with 5 and ≥10 years of experience, respectively) on dedicated 5-megapixel breast imaging displays (MDMG-5221; Barco NV, Kortrijk, Belgium). The radiologists were blinded to the histological results.

All cases without dedicated magnification views were excluded. Cases with grouped amorphous microcalcifications, defined according to the fifth edition of BI-RADS as the most suspicious morphology (i.e., either mammographically or sonographically having a higher BI-RADS score, with category 4C being the most suspicious), were documented by the radiologists. Associated features, including proximity to previous surgical scars, history of or concurrent malignancy, and presence of multiple (≥3) groups of amorphous calcifications in the same quadrant, were also recorded. In the event of any discrepancies, a final decision was

made by a third experienced breast radiologist (with ≥10 years of experience).

Only cases with ≥2 years' follow-up in our institution were included. Final histological diagnosis was obtained from the electronic patient record and based on the highest-grade tissue diagnosis at biopsy or excision. Final statistical database was analysed with SPSS (Windows version 29.0; IBM Corp, Armonk [NY], United States).

RESULTS

A total of 333 cases of mammographically-detected suspicious microcalcifications underwent biopsy in our centre across the 8-year span. Twenty-two cases without dedicated magnification views were excluded. A total of 130 clusters of amorphous microcalcifications in 130 cases were identified. Eight cases with <2 years of follow-up in our institution were excluded (seven benign and one high-risk pathology). One case of invasive ductal carcinoma with architectural distortion as the more suspicious feature was excluded from statistical analysis.

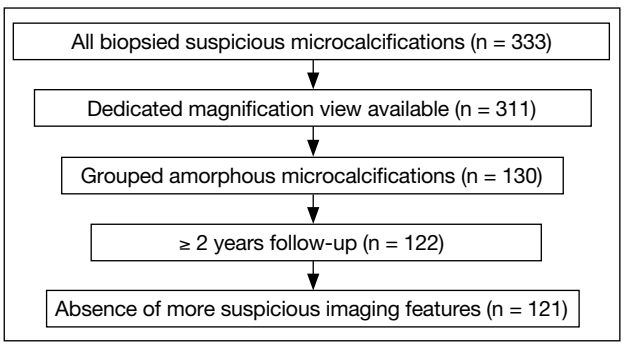

Figure 1. Summary of the cases.

The final study included 121 groups of amorphous microcalcifications in 120 patients (Figure 1). One patient underwent two biopsies 6 years apart, for one group of amorphous microcalcifications in each breast. Both were proven benign. The majority of patients (92.5%) were Chinese and the rest (7.5%) were Pacific Islanders (Table).

Table. Patient demographics, results, and associated features.*

Ethnicity (n = 120)	
Chinese	111 (92.5%)
Pacific Islanders	9 (7.5%)
Age range, y (n = 120)	
≤40	2 (1.7%)
41-50	46 (38.3%)
51-60	47 (39.2%)
≥61	25 (20.8%)
Pathology (n = 121)†	
Benign	105 (86.7%)
No evidence of malignancy	30 (24.8%)
Fibrocystic change	73 (60.3%)
Foreign body granulomatous reaction	1 (0.8%)
Focal ductal hyperplasia	1 (0.8%)
High risk‡	11 (9.1%)
Malignancy	5 (4.1%)
DCIS	4 (3.3%)
Invasive	1 (0.8%)
Associated features	
Adjacent to surgical scars	2
History of/concurrent malignancy	29
Multiple groups of amorphous microcalcifications in the same quadrant	13

Abbreviation: DCIS = ductal carcinoma in situ.
* Data are shown as No. or No. (%), unless otherwise specified.
† Cases of grouped amorphous microcalcifications included in final study.
‡ All are atypical ductal hyperplasia.

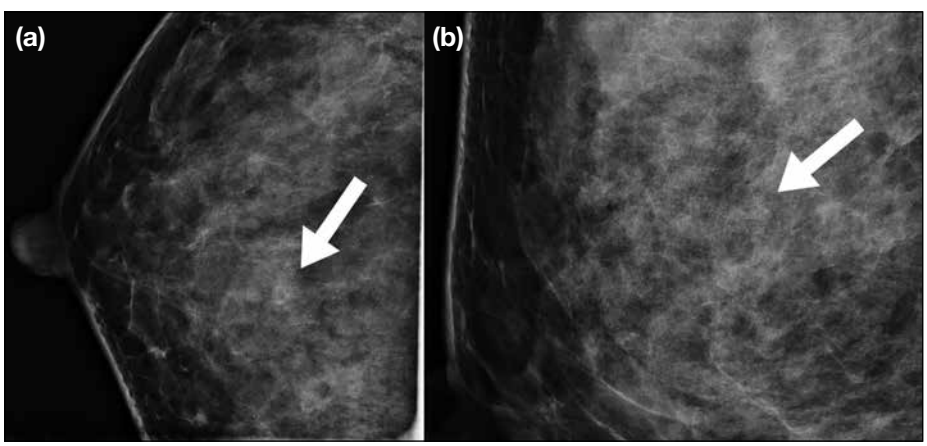

Figure 2. A 41-year-old female's follow-up of bilateral probably benign lesions. (a) Magnified craniocaudal view of the right breast. A group of amorphous microcalcifications (arrow) is faintly observed at middle-to-posterior depth in the central portion. (b) Magnified mediolateral oblique view of the right breast showing corresponding grouped microcalcifications (arrow) at middle-to-posterior depth in the upper portion. Pathology of stereotactic-guided vacuum-assisted biopsy and subsequent mastectomy confirmed ductal carcinoma in situ.

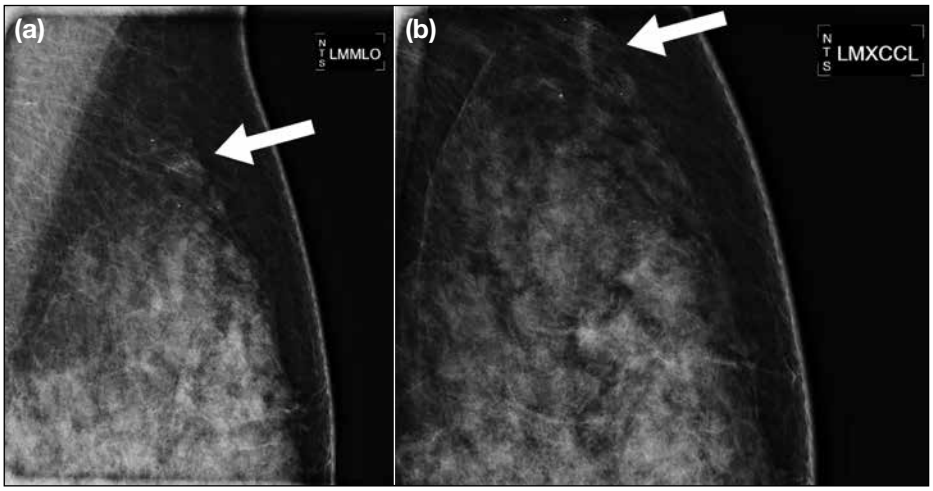

Figure 3. A 52-year-old female's follow-up of bilateral probably benign lesions. (a) Magnified mediolateral oblique view of the left breast. Grouped amorphous microcalcifications newly observed in the upper portion of the breast (arrow). (b) Exaggerated magnified craniocaudal view of the left breast showing corresponding grouped amorphous microcalcifications in the upper outer quadrant (arrow). No sonographic correlate. Pathology of vacuum-assisted biopsy specimen was ductal carcinoma in situ and subsequent excision specimen was upgraded to invasive ductal carcinoma.

Malignancy was found on pathology in 4.1% (n = 5) of the cases. The majority of these cases (80%) came back as ductal carcinoma in situ (DCIS) [Figure 2]. Two cases underwent surgical excision, and two cases underwent simple mastectomy. The remaining case was shown to be invasive ductal carcinoma on the surgical specimen of breast conservation treatment, which was upgraded from DCIS on vacuum-assisted biopsy (Figure 3). It was positive for oestrogen and progesterone receptors and negative for human epidermal growth factor receptor 2.

In all, 9.1% (n = 11) had high-risk pathology and all yielded atypical ductal hyperplasia (ADH) [Table]. Eight cases underwent local excision and two underwent wide local excision. There was no upgrade in the final pathology of any of the 10 cases who underwent surgical excision. One was concluded to have been completely removed by vacuum-assisted excision in a joint clinico-radiological-pathological meeting involving pathologists, radiologists, and breast surgeons. Two cases had the microcalcifications located adjacent to the surgical scars for previous DCIS and invasive tubular carcinoma and came back as benign foreign body granulomatous reaction (Figure 4) and DCIS (Figure 5), respectively.

Within the 2-year follow-up period, there was no recurrence in the malignant and high-risk groups. The grouped macrocalcifications in the benign groups all remained stable. As for the 13 cases with multiple groups of amorphous microcalcifications, the other groups also showed no substantial change, and thus were not rebiopsied.

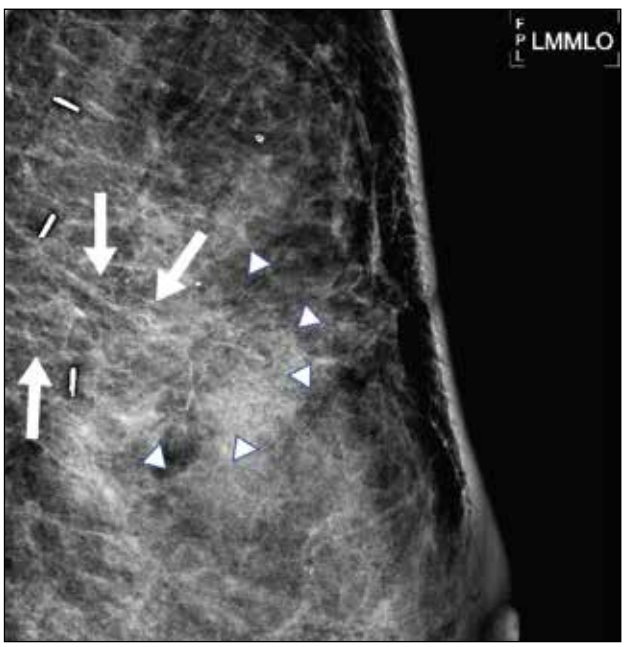

Figure 4. Magnified mediolateral oblique view of the upper left breast in a 55-year-old female patient 1 year after local excision of tubular carcinoma. A new group of amorphous and punctate microcalcifications (arrows) at middle-to-posterior depth adjacent to the surgical scar (arrowheads) was detected. Pathology of the microcalcifications showed benign pathology with a foreign body granulomatous reaction. Follow-up mammograms over 2 years showed no substantial change.

DISCUSSION

Amorphous microcalcifications with grouped distribution are the most common type of suspicious microcalcifications. Studies examining the malignancy rate of grouped amorphous microcalcifications are

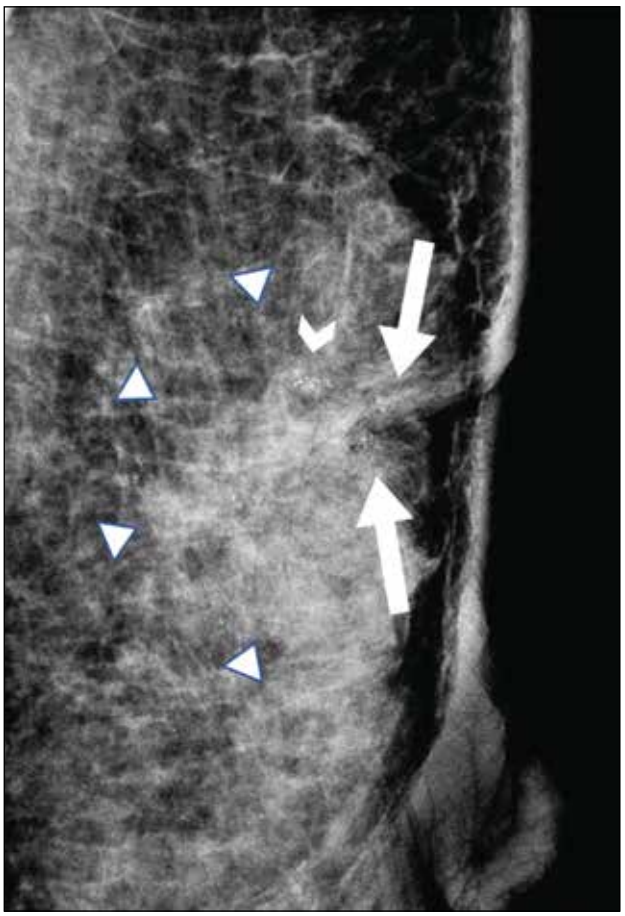

Figure 5. A 46-year-old female with history of left breast conservative treatment for ductal carcinoma in situ (DCIS). Magnified mediolateral oblique view of the upper portion of the left breast 2 years after breast conservation treatment demonstrated a new group of amorphous microcalcifications (arrows) anterior to the surgical site (arrowheads), later confirmed as DCIS on stereotactic-guided vacuum-assisted biopsy. Another group of punctate microcalcifications (notched arrowhead) showed no substantial interval change. A mastectomy was subsequently performed and confirmed no residual malignancy.

limited. The single-institutional retrospective study performed by Iwase et al[4] is by far the relatively more representative one covering the Asian population. Our study sought to reveal the malignancy rate from an 8-year database, with vast majority of Chinese ethnicity, and to compare it with the reported rates of current international studies.

The BI-RADS lexicon was developed by the ACR to standardise the description and management of mammographically detected findings. Various combinations of microcalcification morphology and distribution are subcategorised by their respective malignancy risks, aligned with positive predictive values generated from ACR's national mammography database. BI-RADS category 4A and 4B lesions carry malignancy risks of 2% to 10% and 10% to 50%, respectively.[1] While biopsy is recommended for both subcategories, BI-RADS category 4B lesions commonly require a more comprehensive and meticulous management plan, including rebiopsies in cases of benign pathological findings, or even prophylactic surgical excision subject to multiple factors and patient preference. Other studies[2,4,5] have revealed malignancy rates ranging from 2.8% to 7.6%, which fall within the BI-RADS 4A category. This is in line with the 4.1% malignancy rate (95% confidence interval = 1.4%-9.4%) in our study, comprised of ethnic Chinese and Pacific Islanders.

In recent years, screening programmes advocate a high call-back biopsy rate, arousing controversies on the acceptable malignancy risk and critics on unnecessary biopsies and misallocated healthcare resources.[2,3,6] Apart from recent evidence supporting a lower BI-RADS subcategory as discussed above, the majority of the malignancies come back as DCIS, which is known to carry a high survival rate after surgical and optional adjuvant treatments.[2,3] This is also coherent with our results, with 80% (n = 4) of malignant cases being DCIS. Ongoing prospective trials such as the LORIS trial (LOw RISk DCIS) and the COMET initiative (Core Outcome Measures in Effectiveness Trials) are exploring alternative treatment options including observation.[3] Taking the latest evidence into consideration, a more nuanced management plan may be employed in the future.

Oligane et al[2] showed a higher risk of malignancy when multiple amorphous groups are present in the same quadrant. This feature was absent in the malignant cases from our dataset. There is currently no agreed standard management of the rest of the unbiopsied groups. In our institution, when multiple groups of low-suspicion microcalcifications are present in the same quadrant, the largest group of the most suspicious morphology/distribution combination is targeted for biopsy, as in the previous example in Figure 5. Majewski et al[7] demonstrated a low malignancy rate in secondary biopsy of other morphologically similar group(s) after initial histopathology showing a high-risk lesion, meaning an initial negative biopsy of one group is already useful to predict negative outcome in the others. Hence, we also advocate short follow-up intervals for the other groups

and biopsy only if any increase in extent or suspicion are observed.

Limitations

There are a few limitations to this study. First, as with other published studies, it retrospectively included cases of suspicious microcalcifications from histopathological results. There could be under-called suspicious microcalcifications on initial mammograms not subjected to biopsy. This also raises the issue of inter-reader disagreement, particularly on calcification descriptors such as morphology, as suggested by Lee et al.[8] It is routine practice in our institution to perform a preprocedural joint-specialty review for selected ambiguous cases and for all external referrals to ensure appropriate diagnosis and management.

Second, eight cases were excluded from the final study due to lost or insufficient (<2 years) follow-up after biopsy, with seven benign and one ADH on biopsy. Oligane et al[2] reported a low (2.9%; all to DCIS) surgical upgrade rate for high-risk lesions. In the very unlikely situation that all eight cases turned out malignant 2 years after the biopsy, the overall malignancy rate would be 10% (13/130), falling between the BI-RADS 4A and 4B categories.

Third, our centre does not offer screening services. All screening-detected cases in this study were referrals from outside institutions. Of particular note, our centre has a large volume of surveillance cases with a personal history of breast malignancy or high-risk lesions, and these have been a proven independent predictor of higher malignancy risk by Oligane et al.[2] In our study, 29 cases (24%) of known or concurrent malignancy were included (Table), where two of which were DCIS cases, four of which were ADH, and the rest benign.

Finally, the single-centre setting may limit the external validity of the study.

CONCLUSION

The findings of this study are in line with recent studies and support the BI-RADS category 4A for grouped amorphous microcalcifications. The majority of the malignant lesions also come back as DCIS, which carries a promising post-treatment survival rate. Histological diagnosis remains indicated, yet more nuanced management plans may be implicated in future practice. Further meta-analyses could be directed to exploring differences in malignancy rates across ethnicities, age, and breast density in order to tailor management.

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