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Correlation between the histopathology and the characteristics of mammographic microcalcifications in malignant breast lesions

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Correlation between the histopathology and the characteristics of mammographic microcalcifications in malignant breast lesions

SUMMARY

Purpose: Our aim is to determine whether there is a correlation between the histopathological diagnosis of malignant lesions with mammographic microcalcifications and the characteristics of microcalcifications.

Materials and methods: The patients who underwent mammographic study and the pathologic correlation of malignancy were reviewed retrospectively between October 2007 and April 2011. 43 malignant lesions with microcalcifications at mammography were included in the study. The types and distribution of microcalcifications were assessed according to the ACR BI-RADS (American College of Radiology Breast Imaging Reporting and Data System) classification. In the histopathological evaluation, histopathological type and nuclear grade of lesions and Ductal Carsinoma In-situ subtypes were recorded. The Spearman correlation test and cross tables were used in the statistical analysis.

Results: There were no significance between types of microcalcifications and histopathological type of lesions (p=0,124). There was no significant association between types of microcalcifications and Ductal Carsinoma In-situ subtypes (p>0,05). Lesions that showed segmental distribution or pleomorphic microcalcifications were found in association with nuclear grade 2 or 3. Pleomorphic microcalcifications were seen most frequently in Invasive Ductal Carcinoma (21/26). Besides, a statistically significant correlation was found between the rate of in situ foci in invasive ductal cancer and the microcalcification types (p = 0,044). Since the "r" value was determined as "-0,52", a strong inverse correlation was determined between rate of DCIS and the microcalcification types.

Conclusion: The characteristics of microcalcifications do not clearly indicate the histopathological type. Besides, it should be considered that spontenously resolving microcalsifications may be regarded as a malign finding.

Key Words: *Breast Neoplasm, Calcification, DCIS, Histopathology, Mammography*

Malign meme lezyonlarındaki mikrokalsifikasyonların mammografik görünümünün histopatoloji ile korelasyonu

Amaç: Bu çalışmadaki amacımız, mikrokalsifikasyon içeren malign lezyonların histopatolojisi ile mikrokalsifikasyonların mamografik özellikleri arasında korelasyon olup olmadığını saptamaktır.

Gereç ve Yöntem: Ekim 2007 ve Nisan 2011 tarihleri arasında, radyoloji servisimize başvuran mammografide malignite düşünülen ve patolojide malignite saptanan hastalar retrospektif olarak incelendi. Patolojisi malign çıkan ve mammografide mikrokalsifikasyon içeren 43 lezyon çalışmaya dahil edildi. Mikrokalsifikasyonların dağılımları ve tipleri ACR BI-RADS (American College of Radiology Breast Imaging Reporting and Data System) sınıflamasına gore yapıldı. Histopatolojik değerlendirmede, lezyonların histolojik tipi ve nükleer derecesi ile duktal karsinoma in-situ (DKİS) tipleri kaydedildi. İstatistiksel analizde Spearman korelasyon testi ve çapraz tablolar kullanıldı.

Bulgular: Çalışmada mikrokalsifikasyon içeren malign lezyonlarda mammografik mikrokalsifikasyonların tipi ile lezyonların histopatolojileri arasında istatistiksel anlamlı ilişki bulunmadı (p=0,124). Duktal karsinoma in-situ büyüme paternleri ve lezyonların nükleer derecesi ile mikrokalsifikasyonların tipleri arasında da anlamlı ilişki saptanmadı (p>0,05). Segmental dağılım gösteren lezyonlar nükleer derece-2 veya 3 ile birliktelik gösterdiği bulundu. İnvaziv duktal karsinomda en sık pleomorfik mikrokalsifikasyon saptandı (21/26). Bunun yanında, invaziv duktal karsinomlardaki in-situ fokusların oranı ile mikrokalsifikasyonların tipleri arasında istatistiksel anlamlı ters korelasyon bulundu (p = 0,044). 'r' değeri "-0,52" olup DKIS oranı ile mikrokalsifikasyon tipleri arasında ters yönde ciddi korelasyon mevcuttu.

Sonuç: Malign meme lezyonları içerisindeki mikrokalsifikasyonların özellikleri lezyonların histopatolojik tipini belirlemez. Bunun yanında, spontan ortadan kalkan mikrokalsifikasyonların malign bir bulgu olabileceği bilinmelidir.

Anahtar Kelimeler: *Meme Kanseri, Kalsifikasyon, Histopatoloji, Duktal karsinoma in-situ, Histopatoloji, Mamografi.*

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Introduction

As the most common type of cancer among women, breast cancer maintains its place and significance in terms of mortality and morbidity. Breast calcifications are highly common in mammographic examinations and most of them are benign calcifications; however, calcifications smaller than 1 mm in particular are the most sensitive mammographic findings of early breast cancer.

Mammography continues to be the primary method in screening and diagnosis of breast lesions, with a sensitivity rate of 69-90% (1, 2). Mammography is a radiographic method used worldwide in detection of microcalcifications. The only finding in 70% of in situ carcinoma is microcalcifications (3, 4). Based on the type and distribution of microcalcifications and concomitant findings may be able to comment on whether the lesion is benign or malignant. Thus, unnecessary invasive procedures may be avoided. Therefore, determination of calcifications constitutes an important step of mammographic examination.

Our aim is to determine whether there is a correlation between the histopathological diagnosis of malignant lesions with mammographic microcal cifications and the characteristics of microcalcifications.

Materials and Methods

Patients undergoing mammographic examination in our hospital between October 2007 and April 2011 were retrospectively evaluated. Prior to initiation of the study, ethical committee approval was finalized. A total of 43 lesions which expressed microcalcifications in mammography and diagnosed as malignant in the histopathological evaluation were enrolled in this study.

Mammographic examinations were carried out as screening tests or as diagnostic procedures in suspicious lesions. Examination was performed using a digital mammography device (Selenia Lorad, Hologic Company, Massachusetts, USA). Mammographic examination was carried out at cranio-caudal (CC) and mediolateraloblique (MLO) positions, which is the routine examination protocol. Compression and magnification images were obtained when required The images were interpreted by two experienced radiologists (>10 years experience in breast radiology).

The age range of the patients was 34-75 (mean, 55). Twenty patients (46,5%) did not indicate any symptoms prior to mammography and the examination was carried out as routine yearly mammography controls. On the other hand, 22 patients (51,2%) complained of a palpable painless mass. One patient complained of pain with no mass (2,3%).

The age of the patients, the clinical findings, localization of lesion were recorded. Furthermore, the types and distribution of microcalcifications were assessed according to the ACR BI-RADS (American College of Radiology Breast Imaging Reporting and Data System) classification. Based on the ACR BI-RADS classification, microcalcifications were specified as punctate, amorphous, coarse heterogenous, pleomorphic and fine linear-linear branching types. The distribution of microcalcifications was designated as clustered, multiple clustered, regional, segmental and linear. According to the ACR BI-RADS classification, 23 lesions (53,5%) were evaluated as BI-RADS-5,.while 20 lesions were regarded as BI-RADS 4 (46,5%).

Mammographic examination revealed that 28 of 43 lesions with microcalcifications (65%) were located in the right breast, while 15 lesions (34,9%) were found in the left breast. Twenty nine of the lesions (67%) were detected in the upper-exterior quadrant, 2 lesions (4,7%) in the upper interior quadrant, 2 lesions (4,7%) in the lower exterior quadrant, 5 lesions (11,6%) in the lower interior quadrant, and 5 (11,6%) were located in the retroareolar region. The breast patterns of patients in terms of the ACR BI-RADS classification were as follows: 19 (44%) liposclerosing, 13 (30%) heterogenous dense, 9 (20,9%) lipomatosis, and 2 (4,7%) dense.

Lesions were further assessed by ultrasonography(US). Patients that were found to have a mass ormicrocalcificati-on on US, were subjected to US-guided core biopsy. In patients with no microcalcifications on USG, excisional biopsy was made after stereotactic wire localization or stereotactic-assisted vacuum aspiration biopsy was realized (ATEC stereotactic-guided biopsy system). Following the biopsy procedures, the presence of microcalcifications was confirmed by specimen radiograms. Among the 43 lesions, histopathology was determined via mastectomy material in 23 cases and based on tru-cut biopsy in 19 lesions.

In the histopathological evaluation, the lesions were typed as IDC (Invasive ductal carcinoma), ILC (Invasive lobular carcinoma) and DCIS (Ductal carcinoma in situ). Histopathological nuclear grading was performed in 38 of 43 invasive cancers. The remaining 5 patients were diagnosed solely by tru-cut biopsy; since the operations were performed in another center, a detailed histopathology could not be identified. Comedo, solid, cribriform and mixed type growth patterns were detected in DCIS. The presence and rate of DCIS was assessed in the interior structure of invasive carcinoma.

The histopathological features of the lesions with mammographic features of microcalcifications was statistically compared. The Spearman's correlation test and cross tables were used in the statistical analysis. In the correlation analysis, "r" (correlation coefficient) and "p" values were calculated. "r" values between 0-0,25 were regarded as no correlation, 0,25-0,50 as moderate correlation, 0,50-0,75 as strong correlation, and 0,75-1 as significant correlation. The statistical significance level was specified as $p < 0,05$. Statistical analysis was realized using the SPSS (Statistical Package for Social Sciences) for Windows version 15.0 software.

Results

A mass with irregular borders was observed in 23 lesions (53,5%). Additional finding was not found in 14 lesions including microcalcifications (32,6%). A mass with regular borders was found in 2 lesions (4,7%). The distortion of the parenchyma only was detected in 4 lesions (9,3%). Among the lesions with microcalcifications only (14 lesions), it were diagnosed 6 lesions as DCIS, 1 lesion as lobular invasive cancer, and 7 lesions as invasive ductal cancer.

The types of microcalcifications in malignant lesions exhibited the following features: punctate, amorphous, pleomorphic, fine linear-linear branching, pleomorphic and linear, coarse heterogenous and pleomorphic, amorphous and punctate, and pleomorphic and amorphous (Table 1). In the mixed types, the microcalcifications primarily contained pleomorphic calcifications.

In terms of histopathology, 26 of 43 lesions (60%) were designated as invasive ductal carcinoma, 6 (14%) as lobular carcinoma, and 11(25%) as ductal carcinoma in-situ (Table 2) (Figure 1).

Table1 Microcacification type of lesions

Microcalcification	Number	Percent(%)
Punctate	12	2.3
Amorphous	5	11.6
Pleomorphic	18	41.9
Fine linear-linear branching	12	2.3
Pleomorphic and linear	7	16.3
Coarse heterogenous and pleomorphic	49	9.3
Amorphous and punctate	49	9.3
Pleomorphic and amorphous	37	7.0
Total	43	100

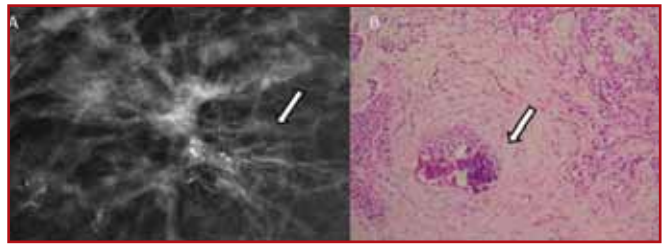

Figure 1. a, b. Case of invasive ductal carcinoma, mammographic (a) and histopathological images (b). A mass, which is forming distortion surrounding parenchymal, and associated linear-linear microcalcifications. Hematoxylin and eosin staining: Magnification 250x.

Table 2 The distribution of histopathological lesions.

Lesions type	Number	Percent (%)
IDC	26	60.5
ILC	6	14.0
DCIS	11	25.6
Total	43	100.0

IDC: Invasive ductal carcinoma, ILC:Invasive lobular carcinoma) and DCIS :Ductal carcinoma in situ.

Distribution of microcalcifications was designated as clustered in 23 cases (53,5%), multiple clusters in 1 case (2,3%), segmental in 18 patients (41,9%) and linear in 1 patient (2,3%). The only case with multiple clustered microcalcifications was diagnosed as invasive ductal carcinoma. The cluster microcalcifications were revealed in 14 of 26 cases (53%) with IDC. The others were revealed the segmental distribution (12/26, %47). Among 6 patients with ILC, clustered distribution was observed in 4 cases, while segmental distribution was found in 2 cases. Furthermore, clustered distribution was seen in 6 of 11 cases with DCIS and segmental distribution was seen in 5 patients.

No statistically significant correlation was found between the distribution of microcalcifications and histopathology of lesions ($p < 0,05$). Among 38 lesions with nuclear grading, while similar rates of clustered and segmental calcifications were observed in lesions of nuclear grade 2 and 3, clustered microcalcifications were found in nuclear grade-1 lesions.

Correlation of the histopathological types of lesions with microcalcification types was evaluated using the Spearman's correlation test; the P value was found as 0,124, indicating a statistically insignificant correlation. In addition, "r" value was calculated as 0,23 and no correlation was found between the histopathological types of lesions and microcalcification types.

Pleomorphic microcalcifications were observed in 21 of 26 cases with IDC, amorphous microcalcifications were found in 3 cases, punctuate type was seen in 1 case, Furthermore, pleomorphic microcalcifications were found in 8 of 11 DCIS cases, while amorphous microcalcifications were observed in 3 patients. Three of the cases with ILC exhibited amorphous microcalcifications and pleomorphic microcalcifications were observed in 3 cases.

Twelve of 22 invasive cancers were indicated as nuclear grade-2, while 3 cases were designated as nuclear grade-3. All of the 5 cases with lobular cancers were specified as nuclear grade-2. Six of 11 DCIS cases were designated as nuclear grade-2, while 5 cases were determined as nuclear grade-3 (Table 3).

Table 3 The relationship between nuclear grade of the lesions with histopathological diagnosis.

Diagnosis	Nuclear Grade			Total
	1.00	2.00	3.00	
DCIS		6	5	11
ILC	0	5	0	5
IDC	2	12	8	2 2
Total	2	23	13	38

IDC: Invasive ductal carcinoma, ILC:Invasive lobular carcinoma) and DCIS :Ductal carcinoma in situ

Upon comparison of the nuclear grading of lesions with microcalcification types, pleomorphic calcifications were observed in 13 cases with nuclear grade-3 lesions. Pleomorphic calcifications constituted 14 of 23 cases with nuclear grade-2 lesions, amorphous microcalcifications were observed in 8 cases and linear-linear branching microcalcifications were found in 1 case. While one of 2 lesions with nuclear grade-1 lesions was designated as punctuate, the other lesion was found to be pleomorphic (Table 4) (Figure 2).

The growth patterns (DCIS subtype) of 11 lesions with DCIS were as follows: comedo in 4 (36,4%), cribriform in 5 (45,5%), and mixed type (comedo+cribriform) in 2 lesions (18,2%) (Figure 3). Correlation of the types of DCIS with microcalcification types was assessed using the Spearman correlation test. The p value was calculated as 0,316, indicating a statistically insignificant correlation. Categorizing the DCIS types as comedo and non-comedo revealed no statistically significant correlation between the types of DCIS and the microcalcification types ($p = 0,20$). Beside, no statistically significant correlation was found between the DCIS types and the nuclear grade ($P = 0,75$, $r = 0,062$).

In 15 invasive ductal cancer cases, the mean rate of ductal carcinoma in situ foci was determined as 30%, with a range of 5-90%. According to the Spearman correlation test, no statistically significant correlation was found between the ductal carcinoma in situ types and the rate of DCIS in invasive ductal cancer ($p = 0,317$). However, a statistically significant correlation was found between the rate of in situ foci and themicrocalcification types ($p = 0,044$). Since the "r" value was determined as "-0,52", a strong inverse correlation was determined between the DCIS content and the microcalcification types.

Discussion

In this study, our aim is to determine whether there is a correlation between the histopathological diagnosis of malignant lesions with mammographic microcalcifications and the characteristics of microcalcifications. However,

Table 4. Comparison of nuclear grade of lesions with type of microcalcifications.

Microcalcifications type	Nuclear grade			Total
	1.00	2.00	3.00	
Punctate	1	0	0	1
Amorphous	0	8	0	8
Pleomorphic	1	14	1	28
Fine linear-linear branching	0	1	0	1
Total	2	23	13	38

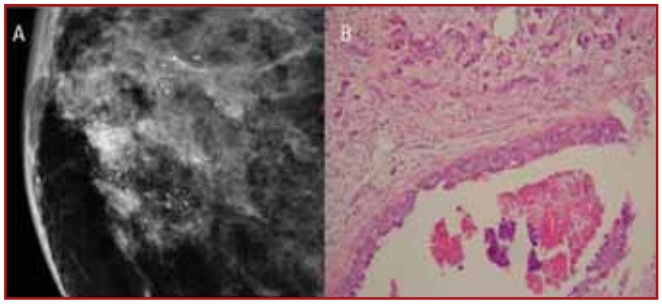

Figure 2. a, b. Mammographic (a) and histopathological images (b). In invasive ductal carcinoma with segmental and multiple cluster pleomorphic microcalsification. Hematoxylin and eosin staining: Magnification 250x.

there were no significance relation between type of microcalcifications and histopathological type of lesions.

In a study conducted by Price and Gibbs on 264 malignant lesions with microcalcifications referred to open surgery, linear and linear branching microcalcifications were found in 51 cases (19%), pleomorphic and coarse heterogenous microcalcifications in 119 patients (45%), and amorphous microcalcifications in 94 cases (36%) (5). However, our results were somewhat different with a high rate of pleomorphic microcalcifications (72,1%) and lower rates regarding other types of microcalcifications. In our study, no significant correlation was determined between the types of mammographic microcalcification and the histopathology of lesions among the malignant lesions containing microcalcifications ($P < 0,05$). Therefore, it was shown that the morphological type of microcalcification is not indicative of the histological type of a lesion; however, pleomorphic microcalcifications were determined to have seen more frequently in IDC and DCIS cases.

The 'National Coordinating Group for Breast Screening Pathology' classified DCIS as high (grade 3), moderate (grade 2) and low (grade 1), based on nuclear grading (6). The results of the current study indicated co-existence of lesions with segmental distribution with nuclear grade-2 or nuclear grade-3. In the literature, the rate of malignancy has been reported as 50-56% in segmental and linear calcifications, as 22% in clustered microcalcifications, and as 0% in regional calcifications (7). The findings in the current study were consistent with the literature. Microcalcifications may be observed in mammography in around 25% of invasive ductal carcinomas (8). It is well known that the rate ofmicrocalcifications increases when the nuclear grade of the invasive ductal cancer increases. In the literature, the rate of microcalcifications has been reported as 36% among the nuclear grade-3 IDC cases, while the rate decreases to 6% in nuclear grade-1 patients (9). In the current study, the frequency of lesions with nuclear grade-2 and grade-3 microcalcifications are similar to the literature. However, in contrast to the literature, nuclear grade-2 lesions were more common in the current study, compared to nuclear grade-3 lesions.DCIS constitutes around 25-30% of all breast cancers. Furthermore, 95% of DCIS cases are diagnosed by the presence of microcalcifications on mammography. In a previous study, the only finding was microcalcification in 151 of 198 cases of in-situ carcinoma (75%), while asymmetric density, a dominant mass and ductographic findings were found in the remaining 25% of cases (10).

In the current study, 6 of 11 cases were found to present with microcalcifications only (54%), with a relatively lower rate compared to that in the literature. This may be due to the low number of cases and no cases of ductography in the current study.

Amorphous and pleomorphic microcalcifications have been reported in nuclear grade-2 lesions in the literature (9, 11). Similarly, in the current study, amorphous microcalcifications were observed in 3 of 6 DCIS cases with nuclear grade-2, and pleomorphic calcifications were found in 3 cases. Lampaje and colleagues reported that lineer-linear branching types microcalcifications frequently associate with nuclear grade-3 lesions (11); however, pleomorphic microcalcifications constituted all DCIS cases of nuclear grade-3 lesions in the current study.

DCIS is categorized according to growth patterns and presence of necrosis. (12). Compared to the non-comedo types (e.g. cribriform, micropapillary, solid), comedo types are more aggressive and have a high recurrence rate; they frequently evolve into invasive cancer (13). In the literature, a correlation was found between the DCIS subtypes and the recurrence rates.

In a study conducted by White et al. (14), the most significant indicator in local recurrence was determined as nuclear grade. In a study carried out by Holland and Hendriks (15), a correlation was determined between the DCIS subtypes and the types of mammographic microcalcifications. In another study, no significant correlation was observed between the mammographic microcalcification types and the nuclear grade (12). Upon classifying our DCIS cases, no statistically significant correlation was found between the DCIS types and the nuclear grade or the types of microcalcification ($p = 0,75$, $p = 0,20$, respectively).

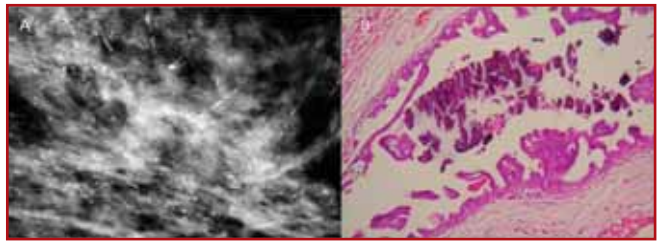

Figure 3. a, b. In case of DCIS, mammographic (a) and histopathological images (b) show segmental pleomorphic and lineer microcalcifications. Hematoxylin and eosin staining: Magnification 250x.

DCIS components may be found in varying proportions more than 75% of invasive ductal cancers (11). In our study, the DCIS component was observed in 15 of 26 IDC cases. The rate of ductal carcinoma in-situ was an average of 30% (range, 5-90%) of 15 invasive ductal cancers. A striking finding was the statistically a strong inverse significant correlation between the rate of in situ foci and the microcalcification types. This finding showed that progresses from linear and pleomorphic types microcalcifications to punctuate microcalcifications is found an increase in rate of DCIS. This finding supports the wiev that it may be regarded as a malignant finding of spontaneously resolving microcalcifications.

The main limitation of the current trial is the low number of cases. Relatively more accurate and reliable results may be obtained with a greater patient sample.

As a result, the characteristics of microcalcifications do not clearly indicate the histopathological type. Besides, it should be considered that spontenously resolving microcalsifications may be regarded as a malign finding.

Declaration of interest: The authors declare no conflict of interest.

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