Original Article

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High-Grade Ductal Carcinoma *In Situ* of the Breast With Regressive Changes: Radiological and Clinicopathological Findings

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ABSTRACT

Objective: Tumour regression is defined as continuity of changes leading to the elimination of a neoplastic population and is reflected as periductal fibrosis and intraductal tumour attenuation. The aim of this study was to describe the radiological and clinicopathological characteristics of high-grade breast ductal carcinoma *in situ* (DCIS) with regressive changes (RC).

Materials and Methods: Thirty-two cases of high-grade DCIS with RC on biopsy specimens followed by excision were included. The mammographic, ultrasonographic (US), and magnetic resonance imaging (MRI) findings of cases were retrospectively reviewed according to the breast imaging reporting and data system (BI-RADS) lexicon. Clinical and histopathological findings [comedonecrosis, estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) status and Ki-67 proliferation index] were recorded. The rate of upgrade to invasive cancer after surgical excision and lymph node involvement were evaluated.

Results: The most common mammographic finding was microcalcifications alone (68.8%). The most frequently seen findings on US were microcalcifications only (21.9%), followed by microcalcifications and hypoechoic area (18.7%). On MRI, most lesions presented as clumped non-mass enhancement with segmental distribution. ER/PR negativity (53.1%, 65.6%), HER2 positivity (56.3%) and high Ki-67 (62.5%), which are known to be associated with more aggressive behavior, were found to be proportionally higher. The rate of upgrade to invasive cancer was 21.8%.

Conclusion: DCIS with RC lesions present most often as microcalcifications alone on both mammography and US. MRI features are not distinguishable from those of other DCIS lesions. DCIS with RC lesions show biomarker status reflecting more aggressive behavior and high upgrade rate to invasive cancer.

Keywords: Ductal carcinoma *in situ*, regressive changes, mammography, ultrasound, breast magnetic resonance imaging

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Key Points

- Ductal carcinoma *in situ* (DCIS) with regressive changes (RC) lesions present most often as microcalcifications alone on mammography and ultrasonographic.
- Magnetic resonance imaging features are not distinguishable from those of other DCIS lesions.
- DCIS with RC lesions show biomarker status reflecting more aggressive behavior and high upgrade rate to invasive cancer.

Introduction

Ductal carcinoma *in situ* (DCIS) of the breast, is intraductal proliferation of malignant epithelial cells which do not pass through the basal membrane (1). DCIS of the breast is a heterogenous lesion group with a broad spectrum of biological behaviour. Compared to low-grade DCIS, high-grade DCIS has more risk of progression to invasive cancer in follow-up resection specimens, axillary lymph node involvement, and recurrence (2-4). Differences between lesions, and the effects of these differences on prognosis are not limited by tumour grade alone. Stromal changes are another of these, which have been defined as regressive changes (RC) and the effect of which on prognosis has been shown in very few publications (5, 6). Tumour regression is defined as continuity of changes leading to the elimination of a neoplastic population. RC has been defined not only in breast cancer but also for several malignancies, such as malignant melanoma, prostate cancer, and cervix cancer. Although not fully understood, regression is believed to represent the host immune system response working to eliminate the neoplastic population (7).

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RC in DCIS of the breast was first described by Muir and Aitkenhead (8) in 1934 and was defined as collagen tissue layers surrounding neoplastic epithelium, interpreted as a part of the scarring/healing process. These changes described in the first studies were thought to be a protective barrier preventing spread of the tumour. However, more aggressive behaviour of cases of DCIS of the breast with RC was shown in later studies (more frequent axillary lymph node involvement and relationship with invasive cancer) causing this to be accepted, not as a protective mechanism, but as a harmful mechanism (5, 6).

An examination of the relevant literature showed that extremely few studies have been conducted related to high-grade DCIS of the breast with RC, and published studies are in the pathology literature (5, 6, 8). Although there are many studies that have examined the imaging findings of breast DCIS, very few studies could be found that have evaluated the imaging findings of a subgroup showing RC. Therefore, the aim of this study was to describe the radiological, including mammography, ultrasonography (US) and magnetic resonance imaging (MRI) and clinicopathological characteristics of high-grade breast DCIS with RC.

Materials and Methods

This retrospective study was approved by the Institutional Review Board of Ege University (21-5.1T/62). As the study was retrospective, informed consent by patients and providers was not required.

Patients

Patients were identified from those who underwent US-guided core biopsy or stereotactic-guided vacuum-assisted core biopsy because of any lesion seen in the breast in examination in the Radiology Department of our hospital between 2016 and 2021, and received a histopathological diagnosis of high-grade DCIS with RC [with or without microinvasion (invasive focus of ≤1 mm)]. Patients were excluded from the study if they had no radiological images before biopsy, if they had a history of breast cancer surgery, or if invasive cancer was diagnosed on biopsy. A total of 32 patients who met the criteria were included in the study. Patient age and gender were recorded in each case.

Radiological Analysis

The findings of all the imaging modalities (mammography, US, MRI) obtained before the biopsy were determined. Evaluation of the findings was made in accordance with the Breast Imaging Reporting and Data System (BI-RADS) version 5.

Mammography in two standard positions (craniocaudal and mediolateral-oblique) was performed using a Selenia Dimensions device (Hologic, Bedford, MA, USA). The mammographic parenchymal pattern was recorded according to the BI-RADS mammographic lexicon. The presence of microcalcification, if any, morphology (amorphous, coarse heterogeneous, fine pleomorphic, fine linear or fine-linear branching) and distribution (diffuse, regional, grouped, linear or segmental) were determined on mammography. Microcalcifications were evaluated according to the presence or absence of accompanying mass, architectural distortion or asymmetry.

US evaluations were performed with a 7-12 MHz linear probe [Siemens Acuson S 2000 (Helx, Evolution), Siemens Medical Solutions Inc, USA]. All of the US records and images which were archived were retrospectively reevaluated. The radiologist was aware of the patients' mammographic results before the sonographic examinations. The sonographic findings were classified as negative in patients who had no findings on US. When microcalcifications were present, the sonographic findings were classified as microcalcifications only, microcalcifications and mass, microcalcifications and architectural distortion, microcalcifications and ductal changes, and microcalcifications and a hypoechoic area. A hypoechoic area was defined as a focal heterogeneity that was different from the surrounding parenchyma or the same area in the ipsilateral breast. Ductal changes were defined as an abnormal caliber, branching of ducts or intraductal echoes. Findings of patients without microcalcification (mass only or architectural distortion only) were also noted.

MRI scans were obtained on a 1.5-Tesla MRI unit (Magnetom Amira, Siemens) or 3-Tesla MRI unit (Magnetom Verio, Siemens) using a dedicated breast coil with the patient in a prone position. Images were acquired in the axial plane with the following sequences: axial, T2-weighted, fat-suppressed, fast spin-echo imaging; pre- and post-contrast, axial, T1-weighted three-dimensional fast spoiled gradient echo sequence. Gadolinium- diethylenetriamine pent acetic acid (Magnevist; Schering, Berlin, Germany) was administered with an intravenous bolus injection at 0.1 mmol/kg. Imaging was performed before the intravenous contrast agent bolus injection and five times after this injection for a period of six minutes. Subtractions of the dynamic contrast enhanced series were obtained by subtracting pre-contrast from post-contrast sequences. Maximum intensity projections were also performed. According to the Fifth edition of the MRI BI-RADS descriptors, the morphology of the lesion was described as mass, non-mass enhancement (NME) and focus. The distribution (focal, linear, segmental, regional, multiple and diffuse) and internal enhancement patterns (homogeneous, heterogeneous, clumped and clustered ring) of NME lesions and the shape (round, oval and irregular), margin (circumscribed and not-circumscribed) and internal enhancement characteristics (homogeneous, heterogeneous, rim enhancement and dark internal septations) of mass lesions were determined.

All mammograms, ultrasonograms, and MRIs were retrospectively reviewed in consensus by one radiologist with 30 years of experience and by one radiologist with seven years of experience in breast imaging.

Clinicopathological Analysis

Clinical features (asymptomatic, palpable mass or nipple discharge) obtained from the referring clinician's records were recorded in each case. The presence or absence of comedonecrosis and expression of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) and Ki-67 proliferation index were recorded. Positive expression for ER/PR status was defined as nuclear staining in 1% or more of tumour cells. Positive immunohistochemistry staining (3+) or HER2 gene amplification by fluorescence *in situ* hybridisation was judged to be HER2 positive. Ki-67 proliferation index was categorised as high if 20% of tumour cells showed staining. Reports from follow-up surgical resections (lumpectomy or mastectomy) after a biopsy diagnosis of high-grade DCIS with RC were reviewed, and the final diagnosis, including the presence or absence of invasive carcinoma and axillary lymph node involvement (if sampled) was noted.

Statistical Analysis

Data analyses were performed using SPSS (SPSS Inc., Chicago, IL, USA) software, version 22.0. Data distributions were evaluated with the Shapiro-Wilk test for normality. All variables without normal

distribution were reported as median and ranges. Normally distributed variables were reported in means and standard deviation.

Results

Radiological Findings of High-Grade DCIS with RC

All patients were female, and the mean age was 55 years (SD, ±13.03; range, 32–78 years) at the time of diagnosis. All patients underwent preoperative mammography. The parenchymal patterns of the breasts were almost entirely fatty in 1 (3.2%) patient, scattered fibroglandular densities in 13 (40.6%) patients, heterogeneously dense in 16 (50%) patients, and extremely dense in 2 (6.2%) patients.

Microcalcifications (30/32, 93.7%) were the most common findings of high-grade DCIS with RC on mammography. Two patients (2/32, 6.3%) presented with other findings; one patient with mass only, and one patient with architectural distortion only. Of the 30 patients with microcalcifcation detected on mammography, 22 (22/32, 68.8%) had microcalcifications only (Figure 1), 6 (6/32, 18.8%) patients had focal asymmetry and microcalcifications (Figures 2, 3), 1 (1/32, 3.1%) patient had a mass and microcalcifications and 1 (1/32, 3.1%) patient had architecural distortion and microcalcifications. The microcalcifications seen in high-grade DCIS with RC were most often of fine pleomorphic morphology with segmental distribution (Table 1, Figure 4).

US was performed in all patients. In 8 of 32 patients (25%), the US examination was negative with no finding observed (Figure 1). The most frequently seen findings were microcalcifications only (7/32, 21.9%) (Figure 5) followed by microcalcifications and hypoechoic area (6/32, 18.7%) (Figure 6). In 5 (5/32, 15.6%) patients, there was a mass and accompanying microcalcifications on US (Figure 2). There was architectural distortion and microcalcifications in 2 patients (2/32, 6.2%) and ductal changes and microcalcifications in 2 (2/32, 6.2%) patients (Figure 4). In the two patients without microcalcifications on mammography, 1 (1/32, 3.1%) was determined with mass only, and 1 (1/32, 3.1%) with architectural distortion only on US (Table 2).

Sixteen of the 32 patients with high grade DCIS with RC underwent breast MRI. The findings of the 16 patients on MRI were a mass in only one patient (1/16, 6.2%) and NME in 15 patients (15/16, 93.8%). One patient with breast mass had irregular shape, irregular margin and heterogeneous internal enhancement characteristics. Most patients had a NME with segmental distribution and clumped internal enhancement characteristics (Figure 4). The MRI characteristics of the patients are shown in detail in Table 3.

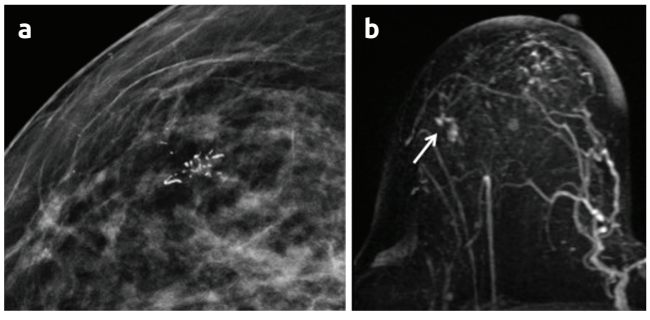

Figure 1. A 69-year-old asymptomatic female patient who presented with microcalcifications detected on screening mammography. a. Mammography image shows pleomorphic grouped microcalcifications. There was no finding on US. b. Axial post-contrast maximal intensity projection MR image shows focal clumped NME (arrow). High grade DCIS with RC was diagnosed using stereotactic-guided vacuum-assisted core biopsy. Both the estrogen and progesterone receptors were negative, HER2 was positive, and the Ki-67 index was more than 20%

US: ultrasonography; MR: magnetic resonance; NME: non-mass enhancement; DCIS: ductal carcinoma in situ; RC: regressive changes; HER2: human epidermal growth factor receptor 2

Clinicopathological Characteristics of High-Grade DCIS with RC

Twenty (20/32, 62.5%) patients were asymptomatic and the lesion was detected on screening mammography, while the remaining 12 (12/32, 37.5%) had symptoms. Of the 12 patients with symptomatic high-grade DCIS with RC lesions, 9 (9/32, 28.1%) had a palpable mass, 1 (1/32, 3.1%) had both a palpable mass and nipple discharge; and 2 (6.3%) had nipple discharge (Table 4).

Histopathological diagnosis was obtained using US-guided core biopsy

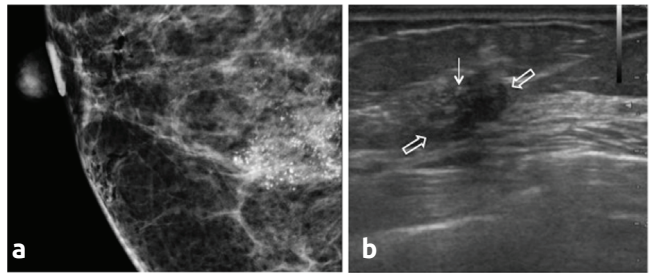

Figure 2. A 45-year-old female patient who presented with a palpable mass. a. Mammography image shows coarse heterogeneous calcifications with segmental distribution and focal asymmetry. b. US image shows irregular, hypoechoic mass with indistinct margins (open arrows). Note the internal bright echoes (arrow) within the mass correspond to microcalcifications on mammography. High grade DCIS with RC was diagnosed using US-guided core biopsy. The lesion was upgraded to invasive ductal carcinoma on surgical excision. Both the estrogen and progesterone receptors were positive, HER2 was negative, and the Ki-67 index was less than 20%

US: ultrasonography; DCIS: ductal carcinoma in situ; RC: regressive changes; HER2: human epidermal growth factor receptor 2

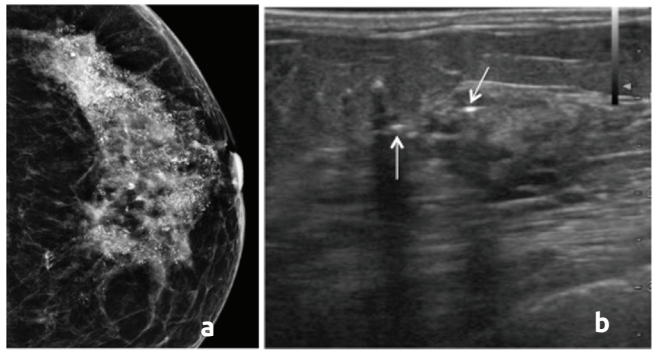

Figure 3. A 55-year-old female patient who presented with a palpable mass. a. Mammography image shows coarse heterogeneous calcifications with diffuse distribution and asymmetry. b. US image shows hypoechoic areas with microcalcifications (arrows). High grade DCIS with RC and with microinvasion was diagnosed using US-guided core biopsy. The lesion was upgraded to invasive ductal carcinoma on surgical excision. Both the estrogen and progesterone receptors were positive, HER2 was negative, and the Ki-67 index was more than 20%

US: ultrasonography; DCIS: ductal carcinoma in situ; RC: regressive changes; HER2: human epidermal growth factor receptor 2

in 24 of 32 patients and using stereotactic-guided vacuum-assisted core biopsy in 8 patients (Figure 7). Comedonecrosis was present in 21 (65.6%) and absent in 11 (34.4%) lesions. ER status was positive in 15 (46.9%) and negative in 17 (53.1%) patients. PR status was positive in 11 (34.4%) and negative in 21 (65.6%) patients. HER2 status was positive in 18 (56.3%) and negative in 14 (43.7%) patients. Ki-67 proliferation index was high (≥20) in 20 (62.5%) and low (<20) in 12 (37.5%) patients.

All patients underwent lumpectomy (n=17) or mastectomy (n=15). The non-palpable lesions were preoperatively localized by mammographically or sonographically guided needle-wire localization technique. When the final histopathology results were reviewed, invasive ductal carcinoma was diagnosed on follow-up surgical resection (lumpectomy or mastectomy) in 7 (7/32, 21.8%) patients. The median size of invasive carcinomas was 4 mm (range, 2-24 mm). Of the seven invasive carcinomas in the cohort, one was T2 and the others were T1 tumors. The median size of DCIS was 20 mm (range, 7–100 mm) in the excision specimens. In addition, microinvasion was detected in the final histopathology in 7 (7/32, 21.8%) patients, although it was not observed on core biopsy. Sentinel lymph node mapping was performed in 22 patients. Axillary lymph node involvement was identified in one (1/32, 3.1%) patient. Clinicopathological characteristics of high-grade DCIS with RC are summarised in Table 4.

Discussion and Conclusion

The incidence of DCIS has increased in parallel with the more widespread implementation of breast cancer screening programs, and now constitutes approximately 20–30% of all breast cancers (9, 10). This increases the importance of knowing the imaging findings of DCIS on all modalities. Many studies have described the radiological findings of low- and high-grade DCIS lesions and the correlation of these findings with the clinicopathological and biologic features of the tumor (11, 12). However, information about DCIS of the breast with RC is mainly limited to the histopathological features of the tumour and the biological behaviour spectrum, and the radiological findings have not been well defined. Therefore, the aim of the current study was to describe the radiological findings of high-grade DCIS with RC, and the results showed that the most common presentation on mammography was in the form of a microcalcification associated lesion (93.8%). In a study by Mun et al. (13), DCIS seen with mammographic calcifications were shown to have more aggressive behavior. In addition, most high-grade DCIS lesions include comedonecrosis and this is a necrotic remnant generally produced by a high-grade tumour undergoing calcification. It has been reported that in low-grade DCIS not including comedonecrosis there is a lower probability of showing microcalcification on mammography and the probability of showing as normal or with non-calcified abnormalities is high (14). The extremely high rate (93.8%) of microcalcifications in the current study can be attributed to all the lesions being high-grade and the majority (65.6%) including comedonecrosis. The most common form of presentation of the calcified lesions in this study was as microcalcifications alone, seen in 68.8% of the patients. As there are few studies in the literature

Table 1. Mammographic characteristics of high-grade DCIS with RC

Findings (n = 32)	n (%)
Lesion type	
• Microcalcifications only	22 (68.8%)
Microcalcifications with	
- mass	1 (3.1%)
- architectural distortion	1 (3.1%)
- focal asymmetry	6 (18.8%)
• Mass only	1 (3.1%)
• Architectural distortion only	1 (3.1%)
Morphology (for microcalcifications)	
• Amorphous	2 (6.7%)
• Coarse heterogeneous	6 (20%)
• Fine pleomorphic	18 (60%)
• Fine linear or fine-linear branching	4 (13.3%)
Distribution (for microcalcifications)	
• Segmental	9 (30%)
• Linear	5 (16.7%)
• Grouped	8 (26.7%)
• Regional	7 (23.3%)
• Diffuse	1 (3.3%)

DCIS: ductal carcinoma *in situ*; RC: regressive changes; n: number of patients

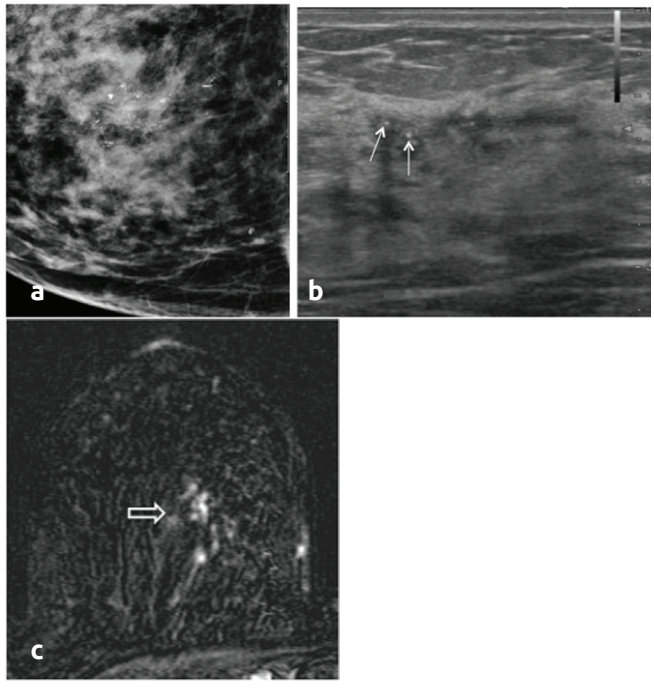

Figure 4. A 48-year-old asymptomatic female patient who presented with microcalcifications detected on screening mammography. a. Mammography image shows pleomorphic microcalcifications with segmental distribution. b. US shows microcalcifications (arrows) within irregularly dilated ducts, which appear as bright intraductal echoes. c. Axial post-contrast subtraction MR image shows clumped NME with segmental distribution (open arrow). High grade DCIS with RC was diagnosed using US-guided core biopsy. Microinvasion was detected on surgical excision. Both the estrogen and progesterone receptors were positive, HER2 was negative and the Ki-67 index was more than 20%

US: ultrasonography; MR: magnetic resonance; NME: non-mass enhancement; DCIS: ductal carcinoma in situ; RC: regressive changes; HER2: human epidermal growth factor receptor 2

examining the imaging findings of DCIS with RC, the results of the present study could only be compared with previous studies of the radiological findings of DCIS cases, which did not examine whether or not they showed RC. Similar to the current study, Scoggins et al. (11) reported that the most frequently seen finding of DCIS lesions on mammography was microcalcifications alone, which was present in 69% of the patients. When the morphology and distribution of the calcifications was examined, the most common were seen to be fine pleomorphic in appearance with diffuse distribution (11). In the current study, the microcalcifcations were similar in morphology, but segmental distribution was more usually seen.

Of all the DCIS with RC cases in the current study, 25% could only be seen on mammography and were occult on US. In the study by Scoggins et al. (11), 48% of the DCIS lesions could not be determined on US and could only be determined on mammography. It has been shown in several studies that approximately 50% of DCIS lesions can be seen on US (15, 16). It has also been reported that there is a higher probability of visualising microcalcifications associated with isolated microcalfications within normal breast tissue has been thought to be more difficult on US (19). This view was supported by the fact that there was no threshold finding such as mass or asymmetry on the mammography of all the patients with negative US in the current study.

The most common US finding of US-visible high-grade DCIS with RC lesions in this study was microcalcifications only, followed by microcalcifications and hypoechoic area. In this study, hypoechoic area was defined as a focal heterogeneity that was different from the surrounding parenchyma. As this term is not found in the BI-RADS sonographic lexicon, several studies have used terms such as non-mass lesion or abnormal-appearing mixed echogenicity, corresponding to non-mass enhancement on MRI (11, 20). When all DCIS lesions are evaluated without grade differentiation, several studies have shown the most common US finding to be mass (21, 22). The US images of high-grade and low-grade DCIS lesions show differences. Cha et al. (20) reported that microcalcification and non-mass lesions on

Table 2. Sonographic characteristics of high-grade DCIS with RC

Findings (n = 32)	n (%)
Negative	8 (25%)
Microcalcifications only	7 (21.9%)
Mass	
• Microcalcifications and mass	5 (15.6%)
• Mass only	1 (3.1%)
Architectural distortion	
• Microcalcifications and architectural distortion	2 (6.2%)
• Architectural distortion only	1 (3.1%)
Microcalcifications and ductal changes	2 (6.2%)
Microcalcifications and hypoechoic area	6 (18.7%)

DCIS: ductal carcinoma *in situ*; RC: regressive changes; n: number of patients

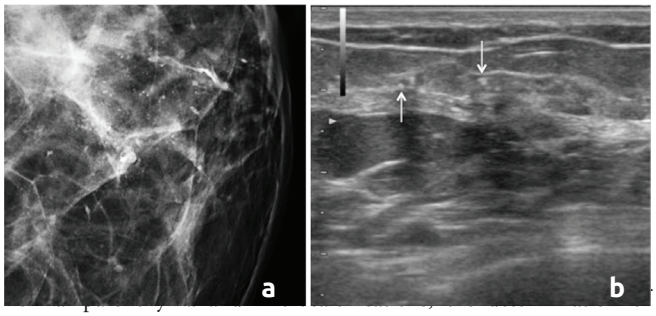

Figure 5. A 46-year-old female patient who presented with bloody nipple discharge. a. Mammography image shows pleomorphic microcalcifications with regional distribution. b. US image shows microcalcifications (arrows) embedded within normal breast tissue (microcalcifications only on US). High grade DCIS with RC was diagnosed using US-guided core biopsy. The estrogen receptor was positive, progesterone receptor was negative, HER2 was positive, and the Ki-67 index was less than 20%

US: ultrasonography; DCIS: ductal carcinoma in situ; RC: regressive changes; HER2: human epidermal growth factor receptor 2

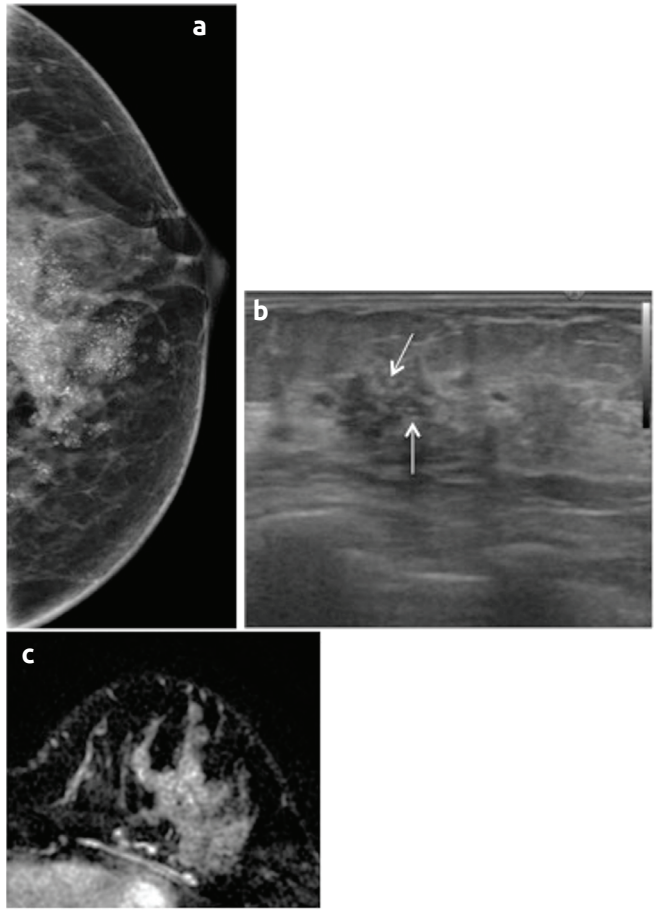

Figure 6. A 45-year-old female patient who presented with a palpable mass. a, Mammography image shows coarse heterogeneous calcifications with regional distribution and asymmetry. b, US image shows hypoechoic areas with microcalcifications (arrows). c, Axial post-contrast subtraction MR image shows NME with heterogeneous internal enhancement in regional distribution. High grade DCIS with RC was diagnosed using US-guided core biopsy. Microinvasion was detected on surgical excision. Both the estrogen and progesterone receptors were positive, HER2 was negative, and the Ki-67 index was more than 20%

US: ultrasonography; MR: magnetic resonance; NME: non-mass enhancement; DCIS: ductal carcinoma in situ; RC: regressive changes; HER2: human epidermal growth factor receptor 2

US were seen more often in high-grade DCIS lesions. Non-calcified abnormalities, such as mass, asymmetry, and architectural distortion, are seen more often in non-high-grade DCIS lesions (17). The US findings of the DCIS lesions with RC in the current study showed similar characteristics to those of high-grade DCIS lesions.

It has been reported that DCIS most commonly manifests as NME (60–81%), and less frequently as a mass (14–41%) or as a focus (1–12%) on MRI (23-25). Only one case in the current study presented in the form of mass and NME presentation was more common than in literature (93.8%). Clumped, followed by a heterogeneous internal enhancement patterns and segmental or linear distribution are hallmarks of NME DCIS on MRIs (26). Similar to the literature, the most common MRI appearance of DCIS with RC in the current study was NME with segmental distribution and clumped internal enhancement characteristics. DCIS with RC did not have a distinct enough appearance to allow it to be differentiated from other DCIS lesions solely on the basis of MRI findings.

Chivukula et al. (5), in their study on high-grade DCIS lesions, showed that RC is a biological change that can lead to invasive cancer with the loss of myoepithelial cells. In the same study, the rate of upgrade to invasive cancer following surgical excision was 20% in the high-grade DCIS with RC group, which was significantly higher than that of the group without RC (4%). In the current study, the rate of upgrade to invasive cancer was similar at 21.8% (7/32) in the final pathology. Furthermore, although microinvasion was not observed in the core biopsy of seven patients in the current study, it was identified as a result of surgical excision. In a study by Zhang et al. (27), DCIS lesions with and without microinvasion were compared, and larger tumour size, high grade, comedo-type, negative PR/ER, high Ki-67 and more axillary lymph node metastasis were present in the microinvasion group. Therefore, if the patients shown to have microinvasion in the final pathology when not observed in core biopsy, were evaluated as upgrade lesions, the upgrade rate in the current study increased to 43.6%. In addition, the rates of axillary lymph node metastasis were determined to be similar in the current study and the study by Chivukula et al. (5) (3.1% and 2.8%, respectively).

When the imaging studies were examined of the seven patients determined with invasive cancer in the current study, in one case presentation was in the form of mass only on mammography, and in four cases there was focal asymmetry accompanying microcalcifications. In other words, of the seven patients with invasive cancer in surgical resection, there were findings other than microcalcification in five (71.4%). Presentation was in the form of microcalcifications alone in two patients. When all the patients included in the study were taken into consideration, of the 10 patients with findings other than microcalcifications only on mammography (microcalcifications with mass, architectural distortion or asymmetry, mass only and architectural distortion only), invasive cancer was identified in follow-up surgical resection in five. The invasive component of the tumour, if present, in DCIS cases cannot usually be found in the microcalcification region, as the invasive component usually presents as mammographic density (mass, architectural distortion or asymmetry) (28). In the current study, 50% of all patients with findings other than microcalcifications on mammography were found to have invasive

Table 3. MRI characteristics of high-grade DCIS with RC

Findings (n = 16)	n (%)
Mass	1 (6.2%)
NME	15 (93.8%)
Distribution (for NME lesions)	
• Focal	1 (6.7%)
• Linear	3 (20%)
• Segmental	8 (53.3%)
• Regional	2 (13.3%)
• Diffuse	1 (6.7%)
Internal enhancement patterns (for NME lesions)	
• Heterogeneous	4 (26.7%)
• Clumped	11 (73.3%)

DCIS: ductal carcinoma *in situ*; RC: regressive changes; n: number of patients; NME: non-mass enhancement; MRI: magnetic resonance imaging

Table 4. Clinicopathological characteristics of high-grade DCIS with RC

Findings (n = 32)	n (%)
Clinical presentation	
• Asymptomatic	20 (62.5%)
• Palpable mass	9 (28.1%)
• Nipple discharge	2 (6.3%)
• Palpable mass+ nipple discharge	1 (3.1%)
Comedonecrosis	
• Present	21 (65.6%)
• Absent	11 (34.4%)
ER status	
• Positive	15 (46.9%)
• Negative	17 (53.1%)
PR status	
• Positive	11 (34.4%)
• Negative	21 (65.6%)
HER2 status	
• Positive	18 (56.3%)
• Negative	14 (43.7%)
Ki-67 proliferation index	
• ≥20	20 (62.5%)
• <20	12 (37.5%)
Upgrade to invasive carcinoma	
• Yes	7 (21.9%)
• No	25 (78.1%)
Axillary node status	
• Positive	1 (3.1%)
• Negative	21 (65.6%)
• Unknown	10 (31.3%)

DCIS: ductal carcinoma *in situ*; RC: regressive changes; n: number of patients; ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor receptor 2

cancer in surgical resection, or 71.4% of patients with invasive cancer in the final pathology had density other than microcalcifications on mammography that confirms that this assumption is also valid for high-grade DCIS with RC. Therefore, in core biopsy, the histopathological diagnosis can be made on the sampled tissue only and this may not represent all the pathological findings of that case.

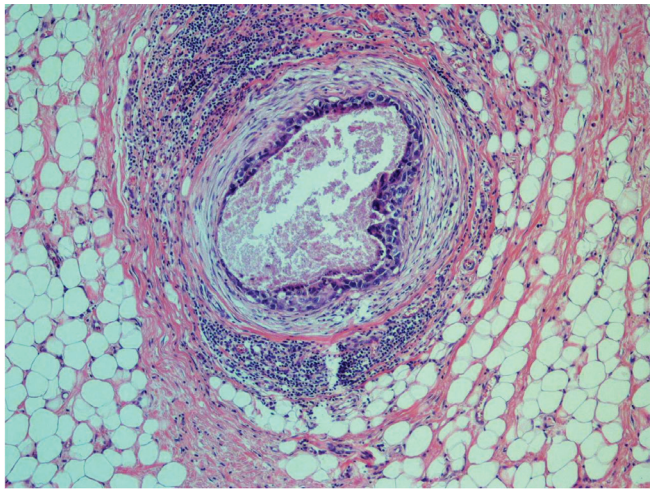

Figure 7. High grade DCIS with RC. Central necrosis and periductal massive fibrosis with lymphocytic infiltration (H&E X 10)

DCIS: ductal carcinoma in situ; RC: regressive changes

In a study by Wasserman and Parra-Herran (6), in which grading was applied according to the severity of RC, it was reported that more advanced RC was more frequent in ER and PR negative tumours. In the same study, despite a tendency to more advanced RC in HER2 positive tumours, the difference was not statistically significant. There is not published study examining the relationship between RC and Ki-67 proliferation index in this type of breast cancer. RCs were not pathologically graded in the current study but in the high-grade DCIS with RC cases included in the study, there were proportionally higher rates of negative ER (53.1%), negative PR (65.6%), positive HER2 (56.3%), and/or high Ki-67 proliferation index (62.5%), which represented more aggressive tumour behaviour. In some studies in the literature, RC are termed neoductgenesis, which is synonymous. Tabar et al. (29) described that neoductgenesis was a typical feature of some high-grade DCIS and was regularly associated with signs of altered epithelial-stromal interaction, like periductal lymphocytic infiltration and remodelling of the specialized periductal stroma. Similar to our study, they also found that neoductgenesis according to their definition correlated with more aggressive tumour biology (30). Wasserman et al suggested that this relationship was due to intrinsic immunogenic characteristics of hormone-negative *in situ* neoplasms and that the immune response leading to RC targetted one or more lineage-specific markers (6). Compared to low or intermediate-grade DCIS, the probability of high-grade DCIS lesions being ER/PR-negative and HER2 positive has been reported to be higher (31). However, whether there is any difference or not between high-grade DCIS with and without RC in respect of biomarkers has not been researched. Therefore, there is a clear need for comparative studies of large series to be conducted.

This study has some limitations. First, it was retrospective in design, so all patients had mammography and US but not all patients underwent breast MRI. Second, the study lacked a control group of patients who were diagnosed with high-grade DCIS without RC. The comparison of the radiological findings of DCIS with and without RC and the correlations of these with histopathological findings would contribute to a clearer determination of lesion character. A further limitation was that the Pathology Department of our hospital has only routinely reported RC seen in DCIS cases in the histopathology reports in the last four years. Therefore, only cases of breast DCIS with RC in the last four years could be included in the study so the sample size was relatively small. However, the study can be considered of value as there are very few studies in the literature that have focused on the radiological findings of DCIS with RC. Nevertheless, there is a need for further studies with larger series on this subject.

In conclusion, to the best of our knowledge, this is one of the few studies to have analyzed the imaging findings of high-grade DCIS with RC and adds to the clinicopathological findings reported by Chivukula et al. (5) and Wasserman and Parra-Herran (6). The results of this study demonstrated that high-grade DCIS with RC presented most often in the form of microcalcifications alone with fine pleomorphic morphology and segmental distribution on mammography. On US, 75% of the lesions could be visualised and the most common appearance was again of microcalcifications alone, followed by microcalcifications and hypoechoic area. On MRI, the most common appearance of DCIS with RC was NME with segmental distribution and clumped internal enhancement characteristics, which is typical for all DCIS lesions. ER/PR negativity, HER2 positivity and high Ki-67, which are known to be associated with more aggressive tumour behavior, were found to be proportionally higher in this study. In addition, upgrade to invasive cancer was made after surgical resection in approximately one in five cases of high-grade DCIS with RC. Knowing the radiological findings of DCIS with RC lesions, which have been shown in a few studies to be associated with more aggressive tumour behavior, will help in the implementation of patient management and treatment planning more safely.

Ethics Committee Approval: This retrospective study was approved by the Institutional Review Board of Ege University (IRB number 21-5.1T/62).

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: A.O., O.A., O.Z.; Concept: M.G., A.O.; Design: M.G., A.O.; Data Collection or Processing: M.G., O.A., O.Z.; Analysis or Interpretation: M.G., A.O., O.A., O.Z.; Literature Search: M.G.; Writing: M.G.

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