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Research

Feasibility of Diffusion-weighted Magnetic Resonance Imaging for Differentiating Idiopathic Granulomatous Mastitis From Malignant Breast Lesions

İdiyopatik Granülomatöz Mastitin Malign Meme Lezyonlarından Ayırılmasında Difüzyon Ağırlıklı Manyetik Rezonans Görüntülemenin Uygulanabilirliği

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ABSTRACT

Objective: Idiopathic granulomatous mastitis (IGM) is an inflammatory breast disease that is often challenging to differentiate from malignancy. This study investigated the role of diffusion-weighted (DW) magnetic resonance imaging in differentiating IGM from malignant breast lesions.

Methods: This retrospective study included 82 female patients with IGM [with a mean age of 33.48 years, minimum (min): 22 - maximum (max): 58 years] and 85 female patients with breast cancer (with a mean age of 48.14 years, min: 31 - max: 79 years). The diagnoses of all patients were confirmed by biopsy, including 114 IGM lesions and 115 malignant lesions in the analysis. DW sequences were acquired with b-values of 0 and 1000 mm^2/sec on a 1.5 T device. The apparent diffusion coefficient (ADC) values of the lesions were measured manually by placing multiple regions of interest of 50-100 mm^2 in the target lesions and contralateral normal parenchyma.

Results: The ADC values of both IGM ($1.119\pm0.454\times10^{-3}$ mm^2/s) and malignant lesions ($1066\pm0.610\times10^{-3}$ mm^2/s) were lower than those of normal parenchyma. The ADC values of the mastitis group were significantly higher than the ADC values of the carcinoma group (p=0.00). The inter-observer (r=0.627) and intra-observer (r=0.775) agreement of ADC measurements were strong.

Conclusion: DW imaging is a useful noninvasive technique to differentiate between IGM and breast carcinoma.

Keywords: Granulomatous mastitis, magnetic resonance imaging, diffusion-weighted MRI, breast carcinoma

ÖZ

Amaç: İdiyopatik granülomatöz mastit (IGM), maligniteden ayırt edilmesi zor olan enflamatuvar bir meme hastalığıdır. Amacımız, difüzyon ağırlıklı (DAG) manyetik rezonans görüntülemenin IGM'yi malign meme lezyonlarından ayırt etmedeki rolünü araştırmaktır.

Gereç ve Yöntem: Bu retrospektif çalışmaya IGM'li 82 kadın hasta [ortalama yaş 33,48 yıl, minimum (min): 22 - maksimum (maks): 58 yıl] ve meme kanserli 85 kadın hasta (ortalama yaş 48,14 yıl, min: 31 - maks: 79 yıl) dahil edilmiştir. Tüm hastaların tanıları biyopsi ile kanıtlanmış olup, toplam 114 IGM lezyonu ve 115 malign lezyon çalışmaya dahil edilmiştir. 1,5 T'de 0 ve 1000 mm^2/sn b-değerlerinde DAG sekansları elde edildi. Lezyonların görünen difüzyon katsayısı (ADC) değerleri, hedef lezyonların ve kontralateral normal parankim içine 50-100 mm^2'lik bir alana sahip multipl ilgi alanları (*regions of interest*) yerleştirilerek manuel ölçüldü.

Bulgular: Hem IGM ($1,119\pm0,454\ x10^{-3}\ mm^2$/s) hem de malign lezyonların ($1066\pm0,610\ x10^{-3}\ mm^2$/s) ADC değerleri normal parankimden daha düşüktü. Mastitis grubunun ADC'leri, karsinom grubunun ADC'lerinden anlamlı derecede yüksekti (p=0,00). ADC ölçümlerinde gözlemciler arası (r=0,627) ve gözlemci içi (r=0,775) güçlü bir uyum vardı.

Sonuç: DAG, ve meme karsinomunu ayırt etmede yararlı, invaziv olmayan bir yöntemdir.

Anahtar Kelimeler: Granülomatöz mastit, manyetik rezonans görüntüleme, difüzyon ağırlıklı MR görüntüleme, meme kanseri

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INTRODUCTION

Idiopathic granulomatous mastitis (IGM) is a benign, recurrent, and prolonged inflammatory disease of the breast. It usually affects women of childbearing age with a history of lactation. Although it is reported to be a rare disease, its prevalence is uncertain. It has been reported to be more common in Hispanic, Asian, and Middle Eastern people, but can be seen in individuals of all races. The most common clinical manifestation of IGM is a unilateral painful, palpable breast mass (1-4). There may also be coexisting palpable axillary lymph nodes, which can be confused with axillary metastatic breast cancer (2-5). The imaging findings are non-specific and vary depending on the stage of the disease and the extent of inflammation (2,5-11). The differential diagnosis of IGM included malignancy and other inflammatory breast diseases. A definitive diagnosis of IGM requires the exclusion of these diseases and histopathological confirmation (2,5,6). Histopathological examination of IGM reveals non-caseating granulomatous inflammation accompanied by lobulocentric acute and chronic inflammatory cells with preserved major ducts and surrounding adipose tissue. Necrosis and fibrosis are less noticeable (12-15).

Diffusion-weighted (DW) magnetic resonance (MR) imaging is a functional modality that allows for the quantitative measurement of the mobility of water molecules *in vivo* to provide numerical data with apparentclear diffusion coefficient (ADC) values without using contrast material. It analyzes the microscopic structure of tissues such as cellularity, membrane integrity, viscosity, organelles, and macromolecules (16). Some studies have found ADC values to be useful for the differentiation between malignant and benign lesions, while others have reported that they are useless due to the significant overlap of ADCs (17).

This study investigated the feasibility of mean ADC values for differentiating IGM from malignant breast lesions.

METHODS

The study was designed as a retrospective study and approved by our University of Health Sciences Türkiye Kartal Dr. Lütfi Kırdar City Hospital Clinical Research Ethics Committee Institutional review board (approval decision no: 514/190/4, date: 25.11.2020). The requirement for obtaining informed consent from the patients was waived.

Study Population

Data of patients who were histopathologically diagnosed with IGM and breast cancer between January 2016 and October 2020 were evaluated. When diagnosing IGM, microbiological tests (gram staining, periodic acid-Schiff and acid-fast staining, mycobacterial cultures, fungal analysis with methenamine silver staining) were carried out to differentiate it from other bacterial and fungal mastitis infections. Moreover, purified protein derivative skin (PPD) test and blood tests were performed for differentiate between tuberculosis mastitis and IGM.

The study included patients with pre-treatment MR examinations. Patients without an MR examination and with postoperative or post-neoadjuvant chemotherapy MR examination, male patients, and patients with images unsuitable for ADC measurement secondary to artifacts were excluded from the study. Lesions smaller than 1 cm were excluded from the study to avoid the partial volume effect. The lesions that were noted on MR examination of patients based on the study inclusion criteria were included in the analysis. In cases of bilateral breast cancer and post-mastectomy recurrent breast cancer in the contralateral breast, ADC measurement was not performed from the contralateral breast parenchyma.

MR Imaging (MRI) Technique

MR were examined on a 1.5 T device (Ingenia Philips Healthcare, Best, the Netherlands). Non-fat-saturated turbo-spin-echo T1 ([field of view (FOV): 302x302 mm, Matrixmatrix: 199x203, flip angle (FA): 90 deg, repetition time (TR): 547 ms, echo time (TE): 8 ms, slice thickness: 3.00 mm, Slice slice gap: 3.30)], spin-echo short tau inversion recovery (FOV: 341x341 mm, Matrixmatrix: 263x223, FA: 90 deg, TR: 4040 ms, TE: 65/175.000 ms, slice thickness: 3.00 mm, slice gap: 3.30), three -dimensional fat-saturated ultrafast spoiled gradient-echo dynamic (FOV: 342x342 mm, Matrixmatrix: 342x340, FA: 10 deg, TR: 5 ms, TE: 3 ms, slice thickness: 2 mm, Sslice gap: 1 mm), and DW (FOV: 364x364, Matrix matrix 151x146, FA: 90, TR: 9400, TE: 71, slice thickness: 3, Slice slice gap: 3) sequences were retrieved. All sequences were acquired in the transverse plane. Dynamic sequences consisted of 5 series, one of which was pre-contrast (90, 142, 194, 246, 298 seconds after injection).

DW sequences were obtained with b-values of 0 and 1,000 mm^2/sec on both devices. All were examined in the prone position using a dedicated 16-channel phased-array breast coil in the prone position. A single dose of 0.1 mmol/kg body weight gadolinium chelate was administered to patients with the aid of an automated injector.

Image Analysis

MR images and ADC measurements were independently assessed by two radiologists (G.R, M.A.), with 6 and 9 years of experience in breast imaging. All MR images

were reviewed in the picture archiving and communication system on the EIZO GS520 workstation. Pre-treatment MR examinations of patients were assessed in both groups. The first group included patients with IGM, whereas the second group included patients with breast cancer. Enhancing masses and non-mass enhancements (NME) were evaluated in patients with IGM. Maximal lesion diameter and average ADC values for IGM and malignant lesions were noted. The maximal lesion diameter was measured in the first post-contrast dynamic series. ADC measurements were carried out in accordance with the recommendations of the European Society of Breast Radiology (18). ADC was measured manually by placing multiple regions of interest (ROIs) with areas ranging from 50-100 mm^2 into the lesion. Multiple ROIs were used as much as they could fit into the lesion. (Figures 1, 2). Other ROIs were obtained by duplicating the first ROI in each lesion. The average of these measurement results was taken for each lesion. In the measurements, the largest visible cross-section of the solid component of the lesions was selected. Dynamic contrast enhanced DCE-MR images were used as references. Measurements were made by placing ROIs in the enhanced parts of the lesions, taking care not to exceed the borders of the lesions. Necrotic and hemorrhagic components were avoided during the measurement. ADC values were also measured from the contralateral normal breast parenchyma in each patient. No measurement was performed from the contralateral parenchyma in patients with previous mastectomy or bilateral breast involvement. The readers were blind to each other's other's results and the patient's patient's diagnosis. After performing ADC measurements for all patients, the readers repeated ADC measurements for the same patients.

Statistical Analysis

The study data were analyzed using the Statistical Package for Social Sciences (SPSS) version 17.0 software. Descriptive statistics are presented as mean, minimum (min), maximum (max), standard deviation, and percentage . The one-sample Kolmogorov-Smirnov test was used to check whether numerical data follow a normal distribution or not. The Mann-Whitney U test was used to compare data that did not show normal distribution (ADCs of lesions and normal parenchyma) between the mastitis and carcinoma groups. Spearman's Spearman's rho test was used to evaluate inter- and intra-observer concordance, which included non-normally distributed parametric data. A p-value <0.05 was considered statistically significant.

RESULTS

Of the 87 patients with IGM, 4 without MR examination and 1 with no ADC measurement secondary to artifacts were excluded from the study. Of the 951 patients with breast cancer, 2 male patients, 828 without pre-treatment MR examination, 28 with post-neoadjuvant chemotherapy MR examination, and 8 with DW images unsuitable for ADC measurement secondary to artifacts were excluded from the study. ADC was not measured from the contralateral normal breast parenchyma in 1 patient with bilateral breast

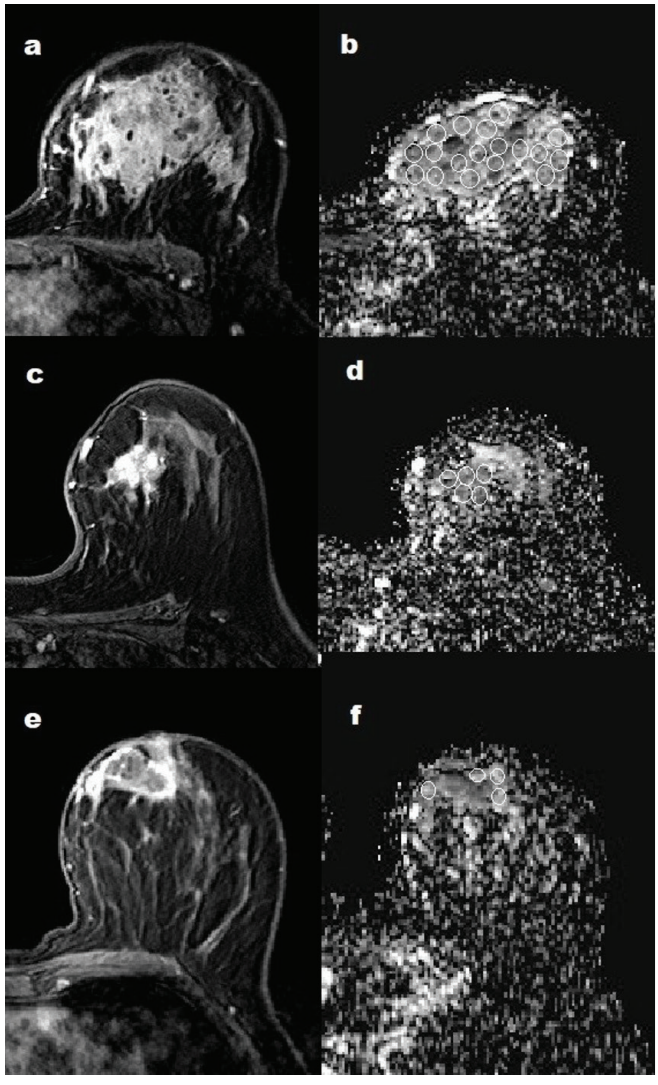

Figure 1. (a, b) The DCE-MR image of a 20-year-old patient with a diagnosis of IGM shows a large area of NME and microabscesses in the left breast. A low signal intensity was measured in this area on the ADC map. (c, d) A 36-year-old patient with a diagnosis of IGM has an enhancing mass lesion in the left breast on DCE-MR image. ADC values were measured from the mass on the ADC map. (e, f) A 42-year-old patient with IGM had a central non-enhancing abscess in the left breast. A low signal intensity is noted in the central part on the ADC map, while a higher signal intensity is visualized on the enhancing wall. ADC measurement was taken from the wall

ADC: Apparent diffusion coefficient, IGM: Idiopathic granulomatous mastitis, DCE-MR: Dynamic contrast-enhanced-magnetic resonance

cancer and in 3 patients who had previously undergone mastectomy.

The study included 82 female patients with IGM (with a mean age of 33.48 years, min: 22 - max: 58 years) and 85 female patients with breast cancer (with a mean age of 48.14 years, min: 31 - max: 79 years). A total of 114 IGM lesions and 115 malignant lesions were assessed.

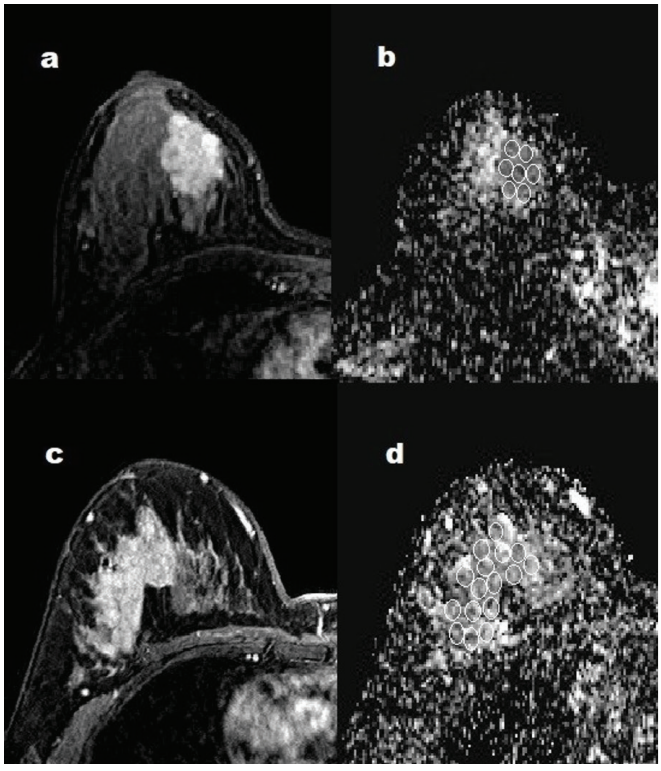

Figure 2. (a, b) The DCE-MR image of a 32-year-old patient with a diagnosis of invasive ductal carcinoma shows an enhancing mass in the right breast. ADC measurement was made from its counterpart on the ADC map. (c, d) The DCE-MR image of a 37-year-old patient; the biopsy result of the NME in the right breast is DCIS. Multiple ROIs were measured from this lesion, which displayed a low signal intensity on the ADC map

ADC: Apparent diffusion coefficient, DCIS: Ductal carcinoma in situ, ROIs: Regions of interest, NME: Non-mass enhancements

According to the histological types, 100 (86.96%) of malignant lesions were NST (no special type), 7 (6.08%) were ductal carcinoma in situ, 6 (5.22%) were lobular carcinomas, and 2 (1.74%) were mucinous carcinoma.

ADC values of both IGM and malignant lesions were lower than those of the normal parenchyma. The ADC values of the mastitis group were significantly higher than the ADC values of the carcinoma group (p<0.0.001) (Table 1). The comparison of the ADC values of abscesses, masses, and NME lesions in the IGM group showed a statistically significant difference between the ADCs of abscesses and the other two lesion groups (p=0.001). However, there was no difference between the ADCs of masses and NME lesions (Table 2). There was no significant difference between the ADCs of mass and NME lesions in the carcinoma group (p=0.8) (Table 3).

There was a strong positive correlation between the ADC measurements made by the first and second observers (r=0.627). A strong positive correlation was found between the intra-observer agreement of ADC measurements (r=0.775).

DISCUSSION

IGM presents with various nonspecific imaging findings and may mimic malignancy and other inflammatory lesions. The most common mammographic findings of IGM include focal

Table 3. ADC values and dimensions of carcinoma lesions by mass and NME subgroups

Carcinoma (n=115)	Mass (n=93)	NME (n=22)	p-value
Lesion size ± SD (mm)	28.49±13.12	37.19±18.06	0.053
Mean ADC (x10^{-3}mm^2/s)	1.072±0.618	1.036±0.589	0.800

ADC: Apparent diffusion coefficient, SD: Standard deviation, NME: Non-mass enhancements

Table 1. Size and ADC values of IGM and carcinoma lesions

Lesion groups	IGM (n=114)	Carcinoma (n=115)	p-value
Lesion size ± SD (mm)	40.15±20.59	30.13±14.46	<0.001
ADC mean ± SD (x10^{-3}mm^2/s)	1.119±0.454	1.066±0.610	<0.001

SD: Standard deviation, ADC: Apparent diffusion coefficient, IGM: Idiopathic granulomatous mastitis

Table 2. Size and ADC values by subgroups of IGM lesions

IGM lesions (n=114)	Abscess (n=54)	NME (n=39)	Mass (n=21)	p-value
Lesion size ± SD (mm)	34.35±22.84	44.74±19.37	46.00±12.05	<0.001
Mean ADC (x10^{-3}mm^2/s)	1.198±0.471	1.066±0.459	1.015±0.381	0.001

SD: Standard deviation, ADC: Apparent diffusion coefficient, IGM: Idiopathic granulomatous mastitis, NME: Non-mass enhancements

or global asymmetry and irregularly shaped mass, with non-specific findings. The ultrasound findings of IGM are irregular hypoechoic mass with tubular extension, heterogeneous hypoechoic mass (or confluent masses) with indistinct, lobulated, or angular margins, and abscess (1,2). Lesions and contrast enhancement patterns, which can also be seen in malignant lesions, have been reported on MRI of IGM. The most common lesions include heterogeneous or ring-enhancing mass lesions and NME. Segmental and regional enhancement patterns have most frequently been reported for NME lesions. Clumped-ring enhancement, which is highly suggestive of malignancy, can also be seen (1,2,5-7).

DW imaging is central to the detection of breast lesions, the differentiation between malignant and benign lesions, the characterization of malignancy, and the evaluation of tumor spread. ADC values of malignant breast lesions have been reported to be lower than those of benign breast lesions (17,18). It has been suggested that low ADC values of malignant tumors are due to increased cell density, larger nuclei, larger macromolecular protein content, and decreased extracellular space (19). Matsubayashi et al. (20) suggested that DW imaging of breast carcinomas was affected not only by cell density but also by structural variations in the stroma (20). Previous studies have found that the ADC values of IGM lesions are lower than those of the normal parenchyma (6,21,22). In line with these studies, the results of this study demonstrated lower ADC values for IGM lesions compared with normal parenchyma. This may be due to the narrowed extracellular space by the dense accumulation of inflammatory cells in the areas occupied by IGM and the viscous inflammation of abscess formations. Additionally, the absence of necrosis in IGM may be the cause of low ADC values.

Kang et al. (23) found that DW imaging was successful in rim-enhancing inflammatory and malignant lesions. In this study, inflammatory breast lesions demonstrated typical central hyperintensity, whereas breast cancers demonstrated peripheral hyperintensity (23). Previous studies have investigated the efficacy of ADC values for the differentiation between mastitis and breast carcinoma (21,24-28). However, the results of these studies are inconsistent, which may be due to differences in patient populations and variations in MR techniques or measurement methods.

According to the results of our study, DWI is useful for distinguishing between IGM and breast carcinoma and may increase the specificity of MR for the diagnosis. A study by Yilmaz et al. (22) comparing ADCs of IGM and malignant breast lesions reported that ADC values failed to differentiate IGM from malignant lesions (22). The reason for different results of our study may be the ADC measurement method. In this study, ROIs were placed only in the viable component of the lesions, excluding necrotic parts. Additionally, the wall of abscess formation containing living tissue was measured, rather than the central pus component. The b-values used in this study may have also affected the results.

In our study, lesion type and ADC values were not correlated in both IGM and malignant lesions, except for abscesses. There is an overlap in ADC values for the differentiation between mass and NME in IGM and malignancy. This result may be attributed to the heterogeneous internal structure of the breast lesions. In this study, DW images were acquired with high b-values (0 and 1000), which were within the recommended range for breast examinations. A high b-value was chosen because of the decreased T2 and perfusion effect and the increased diffusion effect with high b-values.

A limitation of this study is the non-inclusion of b-values. However, a study by Pereira et al. found no benefit of higher b-values in differentiating between breast lesions (24). The retrospective nature of the study is another limitation. The study is limited by not considering the menstrual cycles of the participants, which affects the background contrast when performing MRI.

CONCLUSION

In conclusion, this study compared the ADC values of IGM and malignant breast lesions. The results of the study demonstrated the feasibility of ADC values for distinguishing IGM from malignant lesions. DW-MRI imaging, a non-invasive technique that does not require the use of contrast media, can help differentiate between IGM and breast carcinomas. The advantage of this technique is that DW imaging does not require intravenous contrast media and does not emit radiation.

ETHICS

Ethics Committee Approval: The study was designed as a retrospective study and approved by University of Health Sciences Türkiye Kartal Dr. Lütfi Kırdar City Hospital Clinical Research Ethics Committee (decision no: 514/190/4, date: 25.11.2020).

Informed Consent: The requirement for obtaining informed consent from the patients was waived.

Authorship Contributions

Surgical and Medical Practices: Ş.K., K.Ç., Concept: G.R., M.A., Design: G.R., M.A., N.V., Data Collection or Processing:

G.R., M.A., Ş.K., K.Ç., Analysis or Interpretation: G.R., M.A., N.V., Literature Search: G.R., Writing: G.R.

Conflict of Interest: No conflict of interest was declared by the authors.

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