Combination of elastography and tissue quantification using the acoustic radiation force impulse technology for differential diagnosis of Idiopathic Granulomatous Mastitis with Breast Cancer.

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**Aims and objectives**

Idiopathic granulomatous mastitis (IGM), also called granulomatous lobular mastitis, is a rare chronic benign inflammatory disease with an unknown etiology [1]. Although initially described in 1972 by Kessler and Wolloch [2], the number of cases in the literature remains small. The pathogenesis of IGM is unclear. It is thought to be a localized autoimmune reaction that responds to steroid therapy [3]. The most common clinical presentation is with a unilateral, firm discrete breast mass, which is often associated with inflammation of the overlying skin that can result in nipple retraction and sinus formation. Imaging findings of this condition have been relatively well described by mammography and ultrasonography (US); however, this finding can sometimes be confused with malignancy [4-6].

Acoustic radiation force impulse (ARFI) imaging is a new US based imaging technique used in addition to B-mode US to analyze qualitative visual and quantitative value measurements without compression. It can yield information, not only on the morphologic characteristics but also, on the quantitative value measurements of the mechanical stiffness (elasticity) properties of tissue [7, 8]. Quantitative value measurement is an intrinsic and reproducible property of tissue and tissue quantification. Combined with ARFI technology, quantitative value measurement could generate objective and reproducible data [9]. To our knowledge, the diagnostic performance of this technique in IGM has not yet been evaluated. The purpose of this study was to investigate the clinical use of combination of elastography and tissue quantification using the ARFI technology for differentiation between IGM and malignant breast masses.

**Methods and materials**

**Patients**

This study was approved by the institutional review board and informed consent was obtained from all participants. Between June 2013 and September 2014, a total of 318 consecutive patients who were referred to us with a presumptive diagnosis of a mass underwent elastography and tissue quantification using the ARFI technology after conventional gray-scale US. Then US-guided percutaneous needle biopsy was performed on all patients.

Because our purpose is to make the distinction with IGM and breast cancer, benign lesions and patients with no exact pathologic diagnosis were excluded from the study based on histopathologic evaluation. All malignant lesions (n=74) and IGM lesions (n=46) were included the final study group.
Conventional US, qualitative [Virtual Touch tissue imaging (VTI), Siemens] and quantitative [Virtual Touch tissue quantification (VTQ), Siemens] imaging were performed using the ACUSON S2000 US system (Siemens Medical Solutions, Mountain View, CA, USA).

Conventional Ultrasonography

The descriptive sonographic features of each lesion including margin, shape, size, echo pattern, posterior acoustic features, and distribution were recorded. US findings of the patients were classified according to the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) criteria for US [10].

Virtual Touch tissue Imaging (ARFI elastography)

ARFI is a new tissue strain imaging technology that utilizes sound waves to interrogate the mechanical stiffness properties of tissue [11]. A typical ARFI sequence consists of three pulse types. Initially, a baseline B-mode US reference image of the tissue is obtained via reference pulses. Then, an excitation pulse is applied to generate acoustic radiation force to induce localized deformation. Finally, tracking pulses are used to monitor the deformation response of the tissue. VTI is a qualitative gray scale map of the relative tissue stiffness for a user defined region of interest (ROI). For depicting relative tissue stiffness using VTI, the baseline and post-push signals are compared and differences in the tissue position between relaxed and compressed states are converted to an elastographic image.

The correspondence of the lesions from VTI to those of B-mode images was evaluated. Lesions from B-mode images that failed to be visually confirmed by VTI were classified as pattern 1. Among the lesions that could be visually confirmed, the bright ones were classified into pattern 2 (Fig. 1). Lesions that contained both bright and dark areas were classified into pattern 3 (Fig. 2) and dark lesions were classified as pattern 4. In addition, pattern 4 was subdivided into 4a [dark area in same size as the lesion on the B-mode image (Fig. 3)] and 4b [dark area larger than the lesion on the B-mode image (Fig. 4)].

Virtual Touch tissue Quantification [Shear wave velocity (SWV) measurement]

ARFI technology can also be used for the measurement of shear wave speed [12]. In VTQ, the fixed ROI dimensions of 5 mm x 5 mm are placed on a target region. The reference pulse is used to establish a baseline position of the tissue in the target region. Subsequently, an excitation pulse is applied to generate shear waves. A tracking pulse is applied following the excitation pulse to detect the shear waves and the numeric value of the SWV is calculated in meters per second [11].
The SWV was measured in triplicate for all lesions (internal value). Later, the surrounding tissue and the marginal area of the lesion (marginal value) were included in the ROI, and the SWV was measured (in triplicate). For each region (internal and marginal), the mean SWV value of three measurements was calculated. In some situations such as the heterogeneity of the tissue, the measurements were out of the tolerable range of the system for SWV calculation, so the SWV value was displayed as a non-numeric symbol (X.XX).

All B mode US, VTI, and VTQ examinations were performed by one of two radiologists, each of whom had greater than 6 years' experience in breast sonography.

**Statistical analysis**

The size of the masses and SWV values were numeric variables, so the mean and standard deviation were calculated. The chi-square test was used for analysis of group differences. Internal and marginal SWV values of the lesions were compared between the IGM and malignant lesions by the Mann-Whitney U test and p-values <0.05 was considered statistically significant. We constructed the receiver operator characteristic (ROC) curve and chose the optimal cut-off level to estimate the diagnostic performances of SWV measurements in differentiating IGM and malignant breast lesions. All statistical analyses were performed with SPSS version 11.0 for Microsoft Windows (SPSS Inc., Chicago, IL, USA).

**Images for this section:**
**Fig. 1:** ARFI elastography image of 39-year-old patient with granulomatous mastitis. B-mode image (left) shows a hypoechoic lesion with lobulated margins, ARFI elastography (right) shows a bright area corresponding to the hypoechoic mass (pattern 2).
Fig. 2: ARFI elastography image of 41-year-old patient with granulomatous mastitis. B-mode image (left) shows a hypoechoic lesion with irregular margins. On ARFI elastography (right), bright areas, and dark internal septation (arrow) are detected in the lesion with the dark rim (star) (pattern 3).
Fig. 3: ARFI elastography image of 46-year-old patient with granulomatous mastitis. B-mode image (left) shows a hypo-iso echoic, lobular lesion. ARFI elastography (right) shows a dark area corresponding to the hypo-iso echoic mass. The dark area is in same size with the lesion on the B-mode image (left) (pattern 4a).
**Fig. 4:** ARFI elastography image of 44-year-old patient with invasive ductal carcinoma. B-mode image (left) shows a hypoechoic lesion with irregular margins. ARFI elastography (right) shows a dark area larger than the lesion on B-mode image corresponding to the hypoechoic mass (pattern 4b).
Results

Seventy four patients diagnosed with breast cancer (age range 33-81 years; mean 50 years) and 46 patients diagnosed with IGM (age range 25-57 years; mean 39 years) were included the study. The histological types of malignancy were ductal carcinoma in situ (DCIS) \(n = 6\), invasive ductal carcinoma \(n = 59\), invasive lobular carcinoma \(n = 6\), and malignant epithelial tumor \(n = 3\). The size of the malignant lesions ranged from 8 to 62 mm (mean ± SD, 25.5 ± 10.5 mm) and IGM lesions ranged from 7 to 135 mm (mean ± SD, 43.8 ± 28.1 mm).

Conventional ultrasonography findings

The most frequent US finding of the IGM lesions was identified in 27 patients (58.7%) with solitary or multiple irregular heterogeneous hypoechoic masses, containing tubular extensions across the breast lobules. Six of them had posterior enhancement. Abscess formation and fistula, with echogenic debris surrounded by hyperechoic margins and posterior enhancement, were detected in 13 patients (28.3%). Focal hypoechoic parenchymal heterogeneity with indistinct border was also observed in 6 patients (13 %), while focal breast edema and skin thickening were detected in 9 patients. In addition, moderately enlarged axillary nodes with mild cortical thickening and preservation of hila were detected in 29 (63%) patients. In most of the patients, lesions were located in the upper outer quadrant. The US findings of the 46 IGM lesions were grouped according to the BI-RADS US classification, where the category 3 contained 16 lesions and category 4 had 30 lesions. There was no category 5.

The most frequent US finding of malignant breast lesions was solitary, spiculated or microlobulated, and vertical oriented hypoechoic lesion. Twenty nine of them had posterior acoustic shadowing and 9 had projections from the lesions. US findings of the 74 malignant breast lesions were classified according to BI-RADS US, where category 4 contained 24 lesions and category 5 contained 50 lesions.

ARFI elastography

Two of the IGM lesions were rated as pattern 2 (Fig. 1), 29 as pattern 3 (Fig. 2), and 15 as pattern 4. Seven of the malignant breast lesions were rated as pattern 3 and 67 as pattern 4. Furthermore, we subdivided pattern 4 lesions into 4a and 4b, according to their size difference in ARFI image and B mode image. All of the pattern 4 IGM lesions were rated as pattern 4a (Fig. 3). None of them was rated as pattern 4b. Twenty four of the pattern 4 malignant lesions were rated as pattern 4a and 43 as pattern 4b (Fig. 4).
The difference in the widths of lesions measured on the B-mode and ARFI elastographic images ranged from -3.3 to 1.6 mm (mean: -0.2 ± 1.3 mm) for pattern 4a and ranged from 1.7 to 8.2 mm (mean: 4.6 ± 1.7 mm) for pattern 4b. The capacity of the width difference of the pattern 4 lesions between ARFI elastographic and B-mode images in predicting the presence of malignancy was analyzed using ROC curve analysis. When 0.75 mm was selected as a cut-off level, the sensitivity was 82.1% and the specificity was 100%.

**SWV measurement**

The SWV internal value was measurable within 25 (54.3%) of the 46 IGM lesions and 42 (56.7%) of the 74 malignant breast lesions and the mean internal values of the velocity were 2.80 m/s (range 1.14-4.12, SD = 0.82) and 4.95 m/s (range 2.25-8.02, SD = 1.27), respectively.

The SWV marginal values could be measured all of the IGM and malignant breast lesions and the marginal values of the velocity were 3.39 m/s (range 2.49-5.82, SD = 0.64) and 5.22 m/s on average (range 2.21-8.46, SD = 1.21) respectively. Comparison of the size and internal and marginal shear wave velocities in the IGM and malignant lesions are shown in Table 1.

The capacity of the SWV measurements in predicting presence of malignancy was analyzed using ROC curve analysis. When the higher of the internal and marginal values was adopted and the cut-off level of SWV was set at 4.07 m/s, PPV, NPV, sensitivity, specificity, and accuracy for diagnosing breast masses were 91.8%, 85.1%, 90.5%, 87.0% and 89.1% respectively.

However the mean SWV for malignant lesions classified as pattern 3 or 4a was 5.08 m/s (range 2.21-7.02, SD 1.34) and was 3.49 m/s; (range 2.64-5.82, SD 0.65) for IGM lesions classified into these patterns. When the cut-off level of SWV was set at 4.08 m/s, PPV, NPV, sensitivity, specificity, and accuracy for diagnosing malignancy were 80.6%, 86.4%, 80.6%, 86.4%, and 84%, in pattern 3 and 4a lesions respectively.

The frequency of breast cancer according to BI-RADS US category was 44.4% (24/54) in category 4 lesions in our study. When the higher of the internal and marginal SWV values was adopted and cut-off level was set at 4.08 m/s sensitivity, specificity and accuracy of BI-RADS US category 4 lesions for diagnosing breast masses were 79.2%, 80%, 79.6%, respectively.

**Conclusion**
IGM is a rare chronic benign inflammatory disease [2], which is often confused with malignancy [4-6]. Differentiation of IGM from carcinoma with routine imaging methods like US and mammography is difficult. Therefore new imaging methods are needed. In this study, we investigated the clinical use of a new imaging modality for differentiation between IGM and malignant breast lesions.

In our study, as reported previously [13], the most common US findings were solitary or multiple irregular heterogeneous hypoechoic masses with tubular extensions across the breast lobules. In addition, IGM is significantly larger in size than malignant mass in our study. Unfortunately, these findings are not specific and similar findings can be encountered in the carcinoma. Routine radiological examination such as US and mammography cannot differentiate IGM from carcinoma [14].

Initially, we classified the lesions on the basis of ARFI elastography findings. Most of the IGM lesions were pattern 3 (29/46, 63%). The majority (67/74, 90.5%) of malignant lesions were pattern 4 and 64.1% (43/67) of them were pattern 4b. All pattern 2 (n = 2) lesions were benign, whereas all pattern 4b lesions (n = 43) were malignant. The finding that all 4b lesions were malignant indicates the high clinical significance of pattern 4 subclasses. Because of the peritumoral invasion in malignant lesions, breast cancers would probably exhibit pattern 4b in ARFI elastography [15].

However, width difference of the pattern 4 lesions between ARFI elastographic and B-mode images could be used for predicting the malignancy. When 0.75 mm was selected as a cut-off level, the sensitivity was 82.1% and the specificity was 100% in our study.

The internal SWV could not be measured and expressed as X.XX in 21 (45.6%) of the 46 IGM lesions as well as 32 (43.2%) of the 74 malignant lesions. Mostly, the authors [15, 16] suggest that the reading of ”X.XX” itself is a strong marker of malignancy. Contrary to these studies, we found that 45.6% of the IGM lesions’ SWV values were expressed as non-numeric. In the malignant lesions, technological insufficiency for delineating the high velocity of shear waves, even during passage through hard tissue [16, 17] could result in the disparity. Additionally, in heterogeneous lesions like IGM, it can be due to absorption of the US energy by the tissue [17]. When the SWV value is expressed as X.XX, VTI can be used for determining if the lesion is heterogeneous or hard. In our study, all of the IGM lesions, in which the SWV value was expressed as non-numeric, were pattern 2 and 3. None of them were categorized as pattern 4. Whereas, the malignant lesions in which the SWV value was expressed as non-numeric (22/32, 68.7%) was determined as pattern 4b.

In our study, there was a statistically significant difference in SWV marginal and internal values between the IGM lesions and the malignant lesions (p < 0.001). Furthermore, when the higher of the internal and marginal SWV values was adopted and 4.07
m/s selected as cut-off level, the PPV, NPV, sensitivity and specificity of the SWV measurement for diagnosing breast masses increased.

Combination of VTI and VTQ could be useful in pattern 3 and 4a lesions for benign and malign differentiation. In our study, the mean SWV for malignant lesions classified as pattern 3 or 4a was higher than that for IGM lesions classified into these patterns (p <0.001). When ARFI elastography findings were combined with SWV values, diagnostic sensitivity was 80.6%, specificity was 86.4% and accuracy was 84.0% for pattern 3 and 4a lesions.

The BI-RADS US category 4 assessment covered the wide range of likelihood of malignancy (between 2%-95%). Most of the biopsy recommendations come from this category. Thus, the main focus of researches for early detection of breast cancer should be the BI-RADS US category 4 lesions [18]. In conventional US, low PPVs are more associated with BI-RADS 4 lesions resulting in an increased number of unnecessary biopsies [19]. Gur et al. [20] reported that there was an increase in biopsy rates per screening examination without a corresponding increase in cancer detection rate. These increasing trends in biopsy rates reflect the necessity for a more specific imaging modality. In our study, the frequency of breast cancer according to BI-RADS US category was low (44.4%, 24/54) in the category 4 lesions. When SWV measurement was added and the cut-off level was set at 4.08 m/s, the sensitivity, specificity and accuracy of BI-RADS US category 4 lesions for diagnosing malignancy were 79.2%, 80%, and 79.6%, respectively. Therefore, the combination of ARFI elastography and SWV measurements seems to be useful tools to screen for the necessity of biopsies.

Ito et al. [7] reported in their study that 33% (3/9) of DCIS cases were given benign scores according to the five point scoring system. In our study, all of the DCIS cases (n = 6) were pattern 4a and 50% (3/6) of the cases had benign SWV values. However, a larger study population is necessary to make a more accurate assessment of the usefulness of this technology.

Our major limitation is that, due to we could not change size of the region of interest (ROI), included larger lesions in the study. Because of the large size of the lesions, elastography might be more sensitive in our study.

In conclusion; IGM is often confused with malignancy, and its differentiation from carcinoma with routine imaging methods is difficult. The combination of ARFI elastography and SWV measurement, as a complement to conventional US, provide mechanical properties of tissues, thus have the potential to improve the diagnostic accuracy of US.
Personal information

References