SPANDIDOS PUBLICATIONS

Radiological imaging features of invasive micropapillary carcinoma of the breast and axillary lymph nodes

KEI KUBOTA[1], YASUHIRO OGAWA[1], AKIHITO NISHIOKA[1], YORIKO MURATA[1], SATOSHI ITOH[1], NORIHIKO HAMADA[1], KAZUO MORIO[1], HIRONORI MAEDA[2] and YOSUKE TANAKA[3]

Departments of [1]Radiology and [2]Surgery, [3]Operation Center, Kochi University Hospital, Nankoku, Kochi 783-8505, Japan

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Abstract. Invasive micropapillary carcinoma of the breast is of growing clinical significance. The purpose of this study was to identify the radiological imaging features for this type of breast carcinoma and the axillary lymph nodes. The study population consisted of 30 breast cancer patients (8 invasive micropapillary carcinomas and 22 other types of invasive ductal carcinoma). The breast lesions were evaluated with mammography, ultrasonography, and contrast-enhanced magnetic resonance imaging (MRI) prior to neoadjuvant chemotherapy. The pathological outcome of the axillary lymph nodes in 27 patients was correlated with the sonographic findings. Only contrast-enhanced MRI showed characteristic findings for invasive micropapillary carcinoma. Although invasive micropapillary carcinoma is commonly irregular in shape (7/8) compared with other types of invasive carcinoma (6/22) (p=0.012, χ^2 test), a careful interpretation of radiological imaging to identify lesion borders helped the complete clearance of cancer cells from 6/8 patients with invasive micropapillary carcinoma in one-time breast conservative surgery. The positive and negative predictive values of sonography in diagnosing axillary lymph node metastases in cases of invasive micropapillary carcinoma were 100 and 50%, respectively. In conclusion, contrast-enhanced MRI reveals the irregular shape of invasive micropapillary carcinoma and helps conservative breast surgery to be performed safely. The pathological analysis of axillary nodes in cases of invasive micropapillary carcinoma may prove to be indispensable due to the relatively low negative predictive value of sonography.

Correspondence to: Dr Kei Kubota, Department of Radiology, Kochi University, Oko-cho, Nankoku-shi, Kochi-Prefecture 783-8505, Japan
E-mail: kubotak@kochi-u.ac.jp

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Introduction

Siriaunkgul *et al* first described invasive micropapillary carcinoma (IMPC) as a histological variant of breast cancer in 1993 (1). It is characterized by small, tightly cohesive neoplastic cells disposed within spaces resembling lymphatic vessels. IMPC has a high frequency of axillary node metastases, present in 72.3-100% of cases in some studies (2-4). Thus, IMPC is considered to be an aggressive histological subtype. To the best of our knowledge, the imaging features of this tumor have yet to be compared with those of other types of breast tumors (non-IMPC). Conservative breast therapy is well-established for breast cancer (5-14), with complete excision of the lesion by conservative surgery becoming an important factor in the success of the therapy (15). The diagnosis of axillary lymph node metastases is of great interest to the breast physician (7,15-21). In this study, we retrospectively analyzed a series of breast carcinomas with a variable proportion of IMPC. Our objective was to clarify the differences in imaging features between IMPC and non-IMPC, and to correlate them with local regulation by conservative surgery. We also evaluated the accuracy of ultrasonography (US) in the diagnosis of axillary lymph node metastases.

Materials and methods

We performed a retrospective review of the radiological and clinical findings of 30 invasive breast carcinomas (8 IMPC and 22 non-IMPC) diagnosed in our ultrasound section between April 2002 and September 2003. After imaging, diagnoses of the breast cancer types were confirmed by core biopsy guided by US. The mean patient age was 45.6 (range 39-57) and 52.8 years (range 32-77) for IMPC and non-IMPC, respectively (p=0.08, t-test). The mean size of breast masses was 45.5 (range 15-80) and 19.3 mm (range 14-45) for IMPC and non-IMPC, respectively (p<0.001, t-test). Written informed consent was obtained from all patients.

Image interpretation and data analysis. An evaluation was performed by consensus readings. The images for each modality were evaluated by two radiologists with >10 years of experience. The radiologists were told that the subjects

Table I. Mammographic findings of IMPC and non-IMPC.

	IMPC	Non-IMPC		IMPC	Non-IMPC
Shape (p=0.668)			Margin (p=0.608)		
Round/oval	1	4	Smooth	0	2
Polygonal	1	4	Microlobulated	2	6
Lobulated	2	4	Indistinct	3	5
Irregular	3	3	Spiculated	2	2
Calcification (NA)					
None	3	18			
Round	0	0			
Amorphous	0	0			
Pleomorphic	3	3			
Linear/branched	2	1			

The number of lesions are shown. Data were analyzed by the χ^2 test. NA, statistical analysis is not applicable.

had malignancy, but a detailed diagnosis was not provided regarding whether the lesion was IMPC or a different malignancy. They were blinded to reports from the physical examination and the findings from other modalities. The interpreting radiologists were Y.O. and A.N. for mammography (MMG), K.K. and S.I. for US, and Y.M. and N.H. for MRI.

MMG. MMG was performed in two standard imaging planes (craniocaudal and mediolateral oblique views) using a Senographe DS system (GE Medical Systems, Milwaukee, WI, USA). Lesions visible on the MMG were described using BI-RADS mammographic descriptors of mass shape (round/oval, polygonal, lobulated, or irregular) and margin (smooth, microlobulated, indistinct, or spiculated). The presence or absence of calcification and, if present, the type of calcification (round, amorphous, pleomorphic, or linear/branched) were noted (22).

US. US was performed by one radiologist (K.K.) who was given information regarding tumor location at the time of examination but was blinded to the clinical diagnoses. Each breast mass and the ipsilateral axillary lymph nodes were scanned using a US imaging unit (LOGIQ700MR, GE Medical Systems) with a 7-11 MHz linear-array transducer. US images were stored on a magneto-optical disk and the hard-copy laser images were used for review. Doppler studies were not included in the imaging protocol for this study. The observer was asked to assess the sonographic images using BI-RADS for sonography in terms of mass shape (round/oval or irregular), orientation (parallel or not parallel), margin (circumscribed, indistinct, angular, microlobulated, or spiculated), boundary (abrupt interface or echogenic halo), echo pattern (anechoic, hyperechoic, complex, hypoechoic, or isoechoic) and posterior acoustic features (no posterior acoustic features, enhancement, shadowing, or combined pattern) (23).

Nodes were defined as normal or abnormal on the basis of the criteria of Yang *et al* (17). Patients with at least one metastasis-positive lymph node were classified as node-positive. We defined a normal axillary lymph node on US as an ovoid hypoechoic C-shaped rim of lymphoid tissue surrounding a central echogenic fatty hilum. An abnormal lymph node was rounded and hypoechoic, with or without the associated eccentric cortical hypertrophy and obliteration of the fatty hilum. Size was not used as a criterion for metastatic nodes in this study.

MRI. Dynamic MRI examinations were performed using a 1.5 T unit (Signa Horizon, GE Medical Systems) with subjects in the prone position. After injection of 0.2 ml/kg of gadopentetate dimeglumine, images were acquired in the sagittal plane using the spin-echo technique with fat suppression [repetition time (TR)/echo delay time (TE) = 450/8] and the following imaging parameters: section thickness, 5 mm; gap, 2.5 mm; field of view, 24 cm; and acquisition matrix, 256x192. The MRI findings were classified by the BI-RADS lexicon for MRI: mass shape (round/oval, lobulated, or irregular), margin (smooth, irregular, or spiculated), internal enhancement characteristics (homogeneous, heterogeneous, rim enhancement, dark internal septations, enhancing internal septations, or central enhancement), the initial enhancement phase of the kinetic curve (slow, medium, or rapid), and the delayed phase kinetic curve (persistent, plateau, or wash-out) (24).

Conservative breast surgery. As a rule, tumor excision was performed to include a rim of grossly normal tissue following neoadjuvant systemic chemotherapy. Additional resection was performed if the concurrent rapid pathological analysis during surgery revealed the presence of cancer cells near the edge of the resected specimen. At our institute, neoadjuvant chemotherapy comprised of four cycles of CAF regimen: each dose comprised 600 mg/m^2 of cyclophosphamide, 20-40 mg/body of pirarubicin, and 600 mg/m^2 of 5-fluorouracil, injected intravenously. The patients received neoadjuvant chemotherapy except those with a small primary tumor (<15 mm in diameter) and those aged >75 years. In addition, an intra-arterial (subclavian and internal mammary artery) infusion of epirubicin (40 mg) and 5-fluorouracil (1000 mg) was added between one and three times preoperatively for patients with large breast tumors or bulky axillary lymph node metastases

Ultrasonographic findings of IMPC and non-IMPC.

	IMPC	Non-IMPC		IMPC	Non-IMPC
Shape (p=0.295)			Orientation (p=0.064)		
Round/oval	3	13	Parallel	7	11
Irregular	5	9	Not parallel	1	11
Margin (p=0.169)			Echo pattern (NA)		
Circumscribed	0	1	Anechoic	0	0
Indistinct	3	1	Hyperechoic	0	0
Angular	1	4	Complex	0	1
Microlobulated	4	13	Hypoechoic	8	21
Spiculated	0	3	Isoechoic	0	0
Posterior features (NA)			Boundary (p=0.081)		
No features	6	13	Abrupt interface	4	18
Enhancement	0	5	Echogenic halo	4	4
Shadowing	2	4			
Combined	0	0			

The number of lesions are shown. Data were analyzed by the χ^2 test. NA, statistical analysis is not applicable.

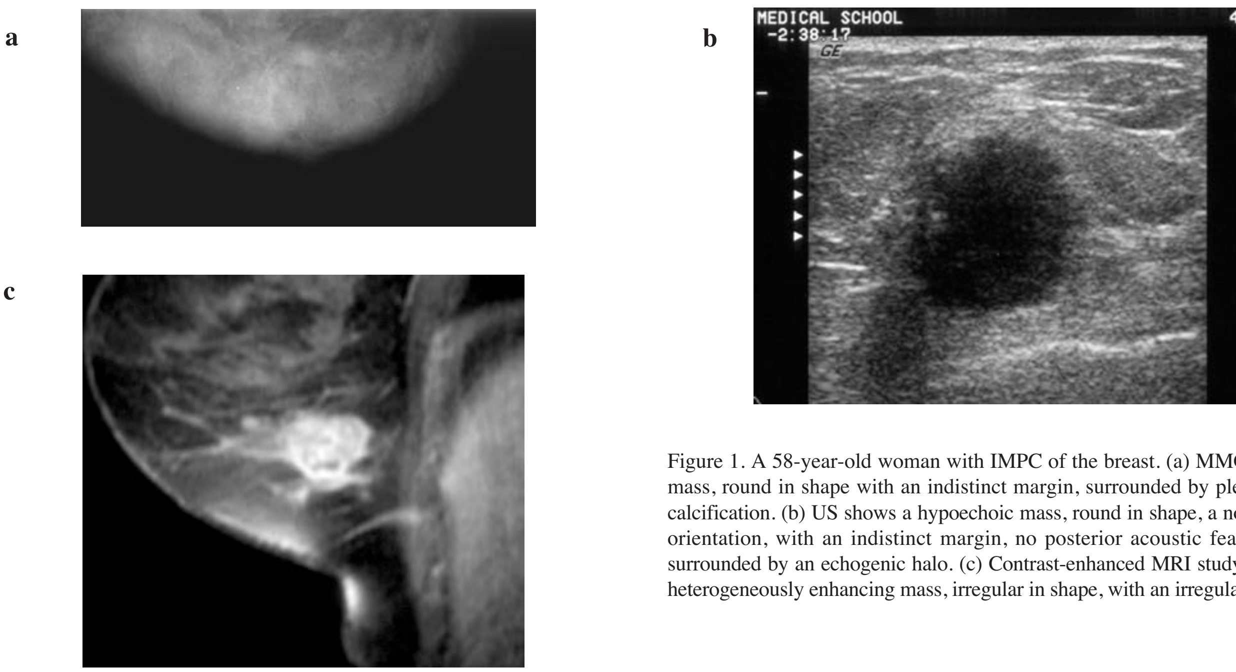

Figure 1. A 58-year-old woman with IMPC of the breast. (a) MMG shows a mass, round in shape with an indistinct margin, surrounded by pleomorphic calcification. (b) US shows a hypoechoic mass, round in shape, a non-parallel orientation, with an indistinct margin, no posterior acoustic features, and surrounded by an echogenic halo. (c) Contrast-enhanced MRI study reveals a heterogeneously enhancing mass, irregular in shape, with an irregular margin.

(no preoperative chemotherapy, n=4; CAF alone, n=5 and CAF plus intra-arterial infusion, n=21).

Axillary pathology. A sentinel node biopsy was performed using the blue dye method immediately before surgery, as described in a previous study (21), for all patients except those clinically node-negative and those who refused node biopsy. After the extirpation of a sentinel node, axillary dissection was performed in the patients, except those who refused axillary dissection in cases where the sentinel node biopsy was negative for metastases. Finally, axillary lymph node pathology was obtained in 27 patients (23 with axillary dissection and 4 with sentinel node biopsy).

Statistical analysis. Data were analyzed using the χ^2 test or t-test. Values of $p<0.05$ were taken to indicate statistical significance.

Results

Primary breast mass. The results of MMG, US and MRI are presented in Tables I, II and III, respectively. Although US and MRI revealed masses in all patients, MMG revealed 22 of the 30 masses (7/8 IMPC and 15/22 non-IMPC). There was no predictive descriptor in the BI-RADS lexicon for IMPC on MMG and US. Shape, one of the BI-RADS descriptors, was the only characteristic finding for IMPC on MRI (Tables I-III).

Table III. MRI findings of IMPC and non-IMPC.

	IMPC	Non-IMPC		IMPC	Non-IMPC
Shape (p=0.012)			Margin (p=0.179)		
Round/oval	0	6	Smooth	1	2
Lobulated	1	10	Irregular	3	16
Irregular	7	6	Spiculated	4	4
Initial kinetic curve (p=0.065)			Delayed kinetic curve (p=0.863)		
Slow	0	1	Persistent	1	3
Medium	0	9	Plateau	4	13
Rapid	8	12	Wash-out	3	6
Internal enhancement (NA)					
Homogeneous	0	5			
Heterogeneous	7	13			
Rim enhancement	1	1			
Dark septations	0	2			
Enhancing septations	0	1			
Central enhancement	0	0			

The number of lesions are shown. Data were analyzed by the χ^2 test. NA, statistical analysis is not applicable.

On MRI, IMPC masses were more frequently irregular in shape compared with non-IMPC masses (Fig. 1).

There was no statistical difference in the rate of positive cancer cells present near the edge of the resected specimen in the first resection (2/8 IMPC and 2/22 non-IMPC, p=0.257, χ^2 test). An additional resection for patients with a positive-margin status in the first resection resulted in a final complete avulsion of the malignancy from the breast in all cases.

Axillary lymph node metastases. The correlation of axillary lymph node US findings and the pathological results of resected specimens are shown in Table IV. The pathological analysis revealed axillary node metastases in 5/8 IMPC and 9/19 non-IMPC cases (p=0.472, χ^2 test, Table IV). The sensitivity, specificity, positive and negative predictive values, and overall accuracy were 40, 100, 100, 50 and 62.5% for IMPC patients, and 66.7, 90.0 85.7, 75.0 and 78.9% for non-IMPC patients, respectively.

Table IV. Correlation between the sonographic findings of axillary lymph nodes and pathological results.

		IMPC		Non-IMPC	
Pathology		+	-	+	-
US	+	2	0	6	1
	-	3	3	3	9
Total		5	3	9	10

+, Lymph node metastases-positive, diagnosed by US or pathological analysis. -, Lymph node metastases-negative diagnosed by US or pathological analysis. The number of patients are shown.

Discussion

Breast physicians have recognized the high incidence of axillary lymph node metastases and the poor prognosis of IMPC patients, as seen in previous reports (1-4). IMPC is considered to have a highly malignant potential. Although the radiological appearance of IMPC had been described by Bilgen *et al*, their experience was limited to MMG and US (25). Moreover, the patient population in their report did not contain cases of non-IMPC, and the BI-RADS lexicon for sonography was not used to characterize IMPC (25). In the present study, we evaluated IMPC using the BI-RADS lexicon for MMG, US, and MRI, which are the essential radiological modalities in breast diagnosis (26-28). The comparison in the present study of IMPC and non-IMPC markedly revealed the features of these breast tumors. IMPC showed a characteristic irregular shape on MRI more frequently than non-IMPC and this MRI lexicon was the only effective descriptor of IMPC. Contrast-enhanced MRI can reveal the increase in the microcapillary bed in breast tumors (26). MRI shows a higher sensitivity than MMG and US for breast cancer (27), and can define the anatomic extent more accurately compared with MMG (28). Contrast-enhanced MRI was an equally reliable modality in evaluating IMPC and non-IMPC.

Cancer cells must be completely excised because local recurrence from a residual lesion can reduce the patient's quality of life (15). However, IMPC has an irregular shape, which is a newly recognized characteristic of the tumor, and has a high likelihood of residual cancer cells in the breast following conservative breast surgery because the tumor unclear. In the present study, a careful interpretation ...gical imaging, including MRI, to identify the lesion boundary and additional resection in the case of a positive margin (cancer cells near the edge of a previously excised specimen) resulted in perfect resection of breast tumors in all cases. IMPC appears to be a good candidate for breast conservative surgery, as are other types of breast cancer. However, the local recurrence and survival rates should be investigated in a future long-term follow-up study.

Concern exists that IMPC has a risk of poor survival as it has a high frequency of axillary lymph node metastases (2-4). In the current study, there was no statistical difference in the incidence of axillary lymph node metastases between patients with IMPC (5/8) and non-IMPC (9/19). An advanced study with a larger number of subjects is needed to determine whether neoadjuvant chemotherapy is related to a lower rate of axillary lymph node metastases and an improved survival prognosis for IMPC patients. The positive predictive value of axillary lymph node metastases was 100 and 85.7% for IMPC and non-IMPC, respectively, while the negative predictive value was 50 and 75% for IMPC and non-IMPC, respectively, which was relatively poor for IMPC patients. The results of the present study suggest that patients with IMPC require a pathological study of axillary lymph nodes regardless of the clinical findings of the nodes.

In conclusion, MRI markedly revealed the characteristic irregular shape of IMPC. A careful interpretation of the radiological findings and a rapid pathological analysis of the resected specimen is helpful for the complete clearance of cancer cells in conservative breast surgery for patients with IMPC. Patients with IMPC may require pathological analysis of the axillary lymph nodes due to the relatively poor negative predictive value of US in diagnosing lymph node metastases.

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