Original

Comparison of Magnetic Resonance Imaging Findings of Neuroendocrine and Non-neuroendocrine Ductal Carcinoma *in Situ* of the Breast

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Abstract : Neuroendocrine ductal carcinoma *in situ* of the breast (NE-DCIS) was recently recognized as a special subtype of DCIS, although the diagnostic criteria for NE-DCIS are yet to be established. DCIS is defined as the immunohisto-chemical expression of neuroendocrine markers chromogranin A and / or synaptophysin in over 50% of tumor cells. Here, we investigated whether there are significant differences in magnetic resonance imaging (MRI) findings between NE-DCIS and non-NE-DCIS. The study sample comprised 8 lesions in 7 patients with breast NE-DCIS and 71 lesions in 69 patients with non-NE-DCIS who underwent preoperative MRI and histopathological diagnosis at our hospital from June 2010 to June 2012. The patients were females aged 34–85 years. We examined the lesion type, pattern of time-signal intensity curve (TIC) on dynamic contrast-enhanced MRI (DCE-MRI), presence or absence of bloody duct ectasia delineation, and presence or absence of calcification on mammography (MMG). Mass-type lesions were significantly more common in breast NE-DCIS than in non-NE-DCIS on MRI. On DCE-MRI, the TIC washout pattern was more commonly observed in NE-DCIS than in non-NE-DCIS, and although there was no significant difference in the rate of bloody duct ectasia delineation, it was relatively more common in NE-DCIS. MMG revealed a significant difference in calcification between non-NE-DCIS (60.1%) and NE-DCIS (0%). Mass-type lesions and TIC washout pattern are significantly more common in patients with NE-DCIS than in those with non-NE-DCIS on MRI and DCE-MRI.

Key words : neuroendocrine ductal carcinoma, breast cancer, magnetic, resonance imaging

Introduction

Neuroendocrine ductal carcinoma *in situ* (NE-DCIS) of the breast was recently recognized as a special subtype of DCIS. Kawasaki *et al*[1)] defined DCIS as the immunohistochemical expression of neuroendocrine markers chromogranin A and / or synaptophysin in over 50% of tumor cells (Figure 1). While there are no established diagnostic criteria as of yet for NE-DCIS, it

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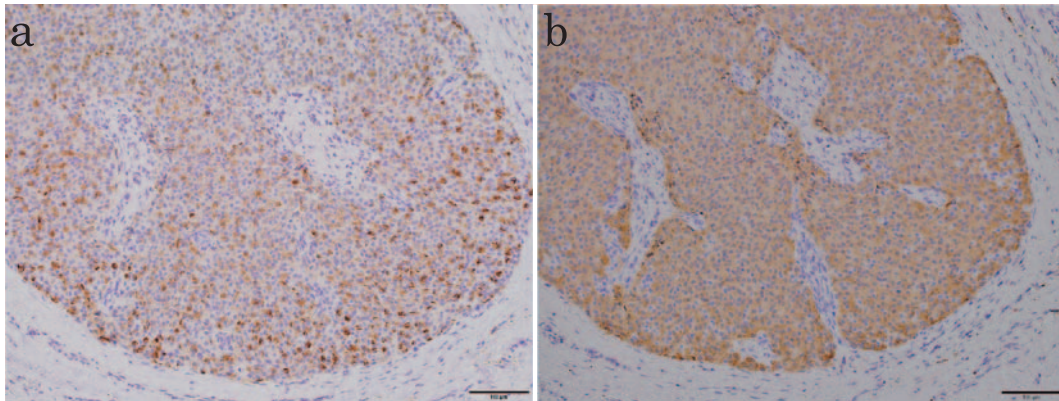[*] To whom corresponding should be addressed.

Fig. 1. Immunohistochemical findings of Neuroendocrine ductal carcinoma *in situ* (NE-DCIS)
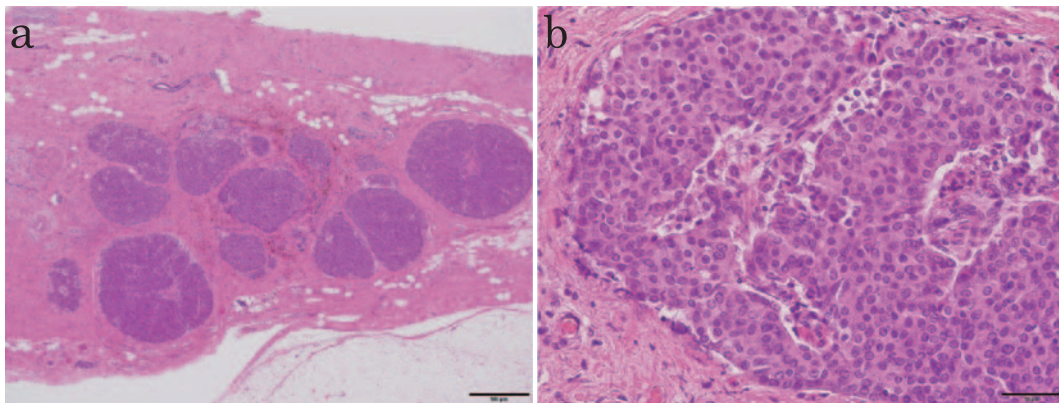a) Chromogranin A, b) Synaptophysin.

Fig. 2. Histological findings of Neuroendocrine ductal carcinoma *in situ* (NE-DCIS)
a) hematoxylin-eosin staining (H&E)× 4, original magnification. Tumor cells are apparent growing solidly in the duct and a well-developed vascular network is evident.
b) H&E × 40, original magnification. Cancer cells with ovoid nuclei showing fine-granular, eosinophilic cytoplasm.

accounts for 6.8% of DCIS cases and is clinically characterized by abundant bloody nipple discharge [2-4].

Several clinicopathological reports of NE-DCIS have described polygonal or fusiform tumor cells exhibiting solid, intraductal proliferation, occasionally accompanied by a vascular network showing hyalinization. The tumor cells possess fine granular cytoplasm and are often eosinophilic, with nuclei characterized by poor atypia and fine granular chromatin (Figure 2)[5].

To our knowledge, very few studies have reported on the magnetic resonance imaging (MRI) findings of NE-DCIS. We therefore investigated whether patients pathologically diagnosed with breast NE-DCIS could be distinguished from those with non-NE-DCIS on preoperative MRI.

Subjects and methods

This study design was clinical research using opt-out and was approved by the ethics review board for clinical research of Showa University Hospital. Of 100 patients in whom 103 lesions

were pathologically diagnosed as DCIS using preoperative MRI in the period from June 2010 to June 2012, 21 patients who underwent biopsy using stereotactic vacuum-assisted breast biopsy (ST-VAB) prior to MRI and 3 in whom the lesion could not be identified using MRI were excluded. The study analysis therefore comprised 79 lesions from 76 patients.

We used the 1.5 Timager Signa System (General Electric, Yokogawa Medical Systems, Japan) for MRI, with patients in the prone position and imaging performed according to the conditions described in Table 1A for the period of 2008−2011 and Table 1B for 2012. Gadolinium-DTPA (Magnevist ; Schering, Berlin, Germany) was used as the contrast agent, with 10 ml intravenously injected, followed by a 10 ml flush with physiological saline.

MRI was used to determine the lesion type (mass, non-mass, or focus), time–signal intensity curve (TIC) pattern (washout, plateau, or persistent) on dynamic contrast-enhanced MRI (DCE-MRI, as explained later), and existence of bloody duct ectasia delineation using high-signal intensity on precontrast T1-weighted imaging. The existence and extent of calcification was determined on mammography (MMG).

MRI was used to determine the lesion characteristics such as morphology, but also on the extent and pattern of vascularity with the use of contrast medium. The TIC on DCE-MRI is obtained by repeated MRI scans after contrast injection and is a useful tool for breast cancer diagnosis. In this technique, the shape of the time signal strength curve is usually classified into three types : persistent strengthening, plateau, or washout. A persistent curve showing a sustained increase in signal intensity after contrast injection correlates with a benign lesion, while a plateau curve showing a slow or rapid increase in the beginning followed by a sharp bend and plateau is indicative of malignancy. A washout curve showing a rapid initial rise followed by a drop-off in signal intensity with time is considered relatively specific for malignant lesions[6]. Fisher's exact test (a level of significance of 5%) was used to determine the significance of intergroup differences.

Results

The sample included 79 lesions from female patients aged 34−85 years (mean age, 53.7 years). Of these, 8 lesions in 7 patients were consistent with NE-DCIS (age, 39−69 years ; mean age, 57.3 years), whereas 71 lesions in 69 patients were non-NE-DCIS (age, 34−85 years ; mean age, 53.3 years ; Table 2). Based on MRI, the lesion type for NE-DCIS was mass in 5 (62.5%) patients, non-mass in 2 (25%), and focus in 1 (12.5%), whereas for non-NE-DCIS, the lesion type was mass in 12 (16%) patients, non-mass in 54 (76.1%), and focus in 5 (7.0%). This indicated that mass-type lesions were significantly more common in NE-DCIS cases and non-mass-type lesions were significantly more common in non-NE-DCIS ($P = 0.007$). On DCE-MRI for NE-DCIS patients, TIC showed a washout pattern in 7 (87.5%) patients and a plateau in 1 (12.5%), and none exhibited the persistent pattern, while for non-NE-DCIS, TIC showed a washout pattern in 27 (38.0%) patients, a plateau in 20 (28.2%), and a persistent pattern in 24 (22.8%). The washout pattern was thus significantly more common in NE-DCIS patients. ($P = 0.023$). A case of NE-DCIS is presented in Figure 3a−c, depicting the most common mass-type lesion with TIC washout pattern on DCE-MRI. Figure 3d−f shows a case of non-mass-type lesion showing

Table 1. MRI scanning conditions

A : 2008−2011 breast MRI scanning conditions

Scanning method	Image section	Sequence	TR (ms)	TE (ms)	FA (°)	FOV (mm)	Matrix	Slice thickness (mm)	Slice addition	Number	Scan duration
T2WI (Bilateral)	Sagittal	2D-FSE	3,500	102	90	180	256×224	3	30	2	2'13"
Dynamic FS T1WI (Bilateral) 0 s, 1 min, 2 min, 8 min	Sagittal	VIBRANT	4.5	2.1	12	200	256×206	2.4	128	1	1'30"

B : 2012 breast MRI scanning conditions

Scanning conditions	Image section	Sequence	TR (ms)	TE (ms)	FA (°)	FOV (mm)	Matrix	Slice thickness (mm)	Slice addition	Number	Scan duration
T2WI (bilateral)	Axial	FRFSE-XL	3,800	102	90	350	448×256	2	90	2	4'57"
FS T2WI (bilateral)	Axial	FRFSE-XL	4,400	102	90	350	448×256	2	90	2	5'31"
Dynamic FS T1WI (bilateral) 0 s, 45 s, 2 min 15 s, 8 min	Axial	VIBRANT	6.1	2.98	10	350	384×256	1.6	248	-	1'33"

Table 2. MRI and MMG findings

|		DCIS n = 71	NE-DCIS n = 8	P
MRI findings				
	Lesion type			
	Mass	12 (16.9%)	5 (62.5%)	
	Non-mass	54 (76.1%)	2 (25.0%)	0.007
	Focus	5 (7.0%)	1 (12.5%)	
	TIC pattern on DCE-MRI			
	Washout	27 (38.0%)	7 (87.5%)	
	Plateau	20 (28.2%)	1 (12.5%)	0.023
	Persistent	24 (33.8%)	0 (0.0%)	
	Duct ectasia			
	(+)	18 (25.0%)	4 (50.0%)	0.21
	(−)	53 (75.0%)	4 (50.0%)	
MMG				
	Calcification			
	(+)	43 (60.1%)	0 (0.0%)	0.002
	(−)	28 (39.1%)	8 (100%)	

DCE-MRI : dynamic contrast-enhanced MRI, MMG : mammography, MRI : magnetic resonance imaging, TIC : time−signal intensity curve
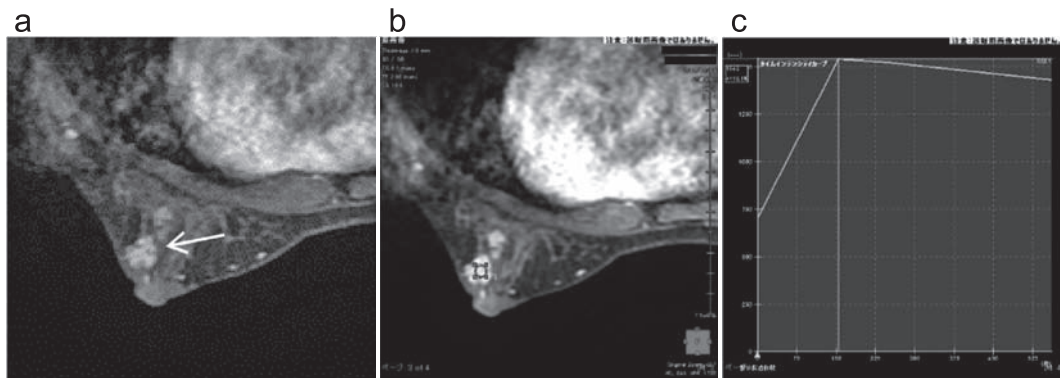
Female, 40 years of age, mass-type
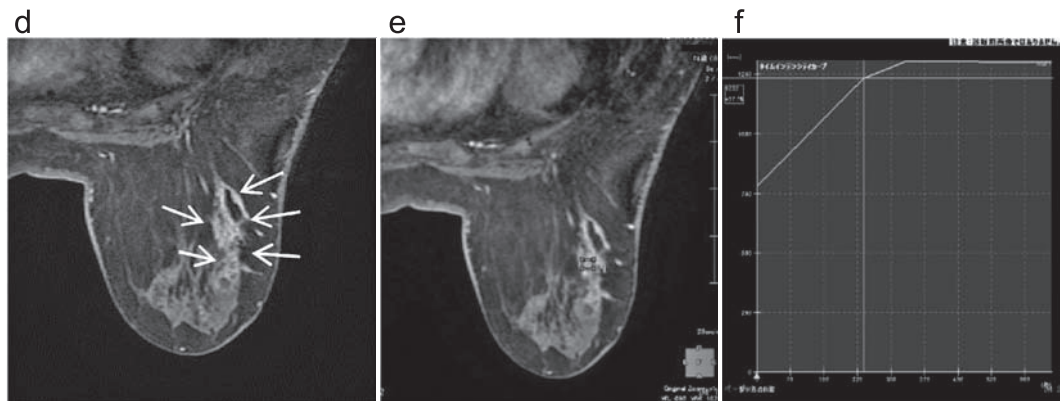
Female, 74 years of age, non-mass-type
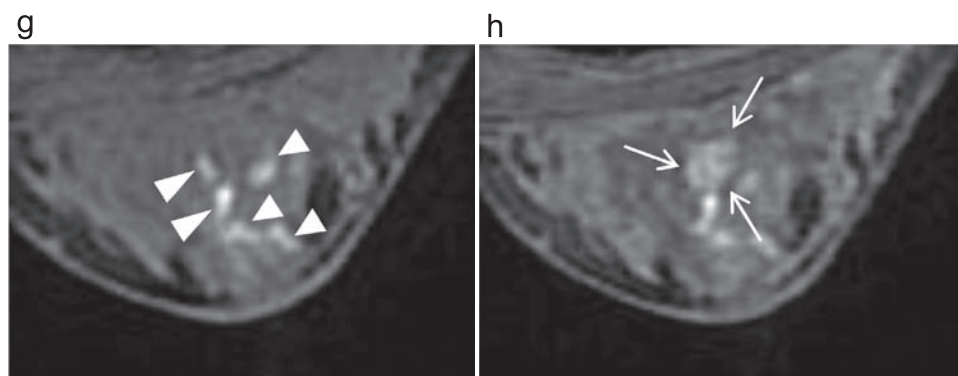
Female, 39 years of age, Case showing bloody duct ectasia

Fig. 3. Neuroendocrine ductal carcinoma *in situ* (NE-DCIS) case

Female, 40 years of age, mass-type
Dynamic FS T1WI axial image : a) contrasting at 1 min, b) contrasting at 8 min, c) time-signal intensity curve (TIC). In a-c, the left breast shows contrast enhancement of a mass-type lesion (a : arrow). On dynamic contrast-enhanced (DCE)-MRI, TIC shows a washout pattern.
Female, 74 years of age, non-mass-type
Dynamic FS T1WI axial image : d) 1 min, e) 8 min, f) time-signal intensity curve (TIC). In d–f, the right breast shows contrast enhancement of a non-mass-type lesion (d : arrows), and on dynamic contrast-enhanced (DCE)-MRI, TIC shows a plateau pattern, as the only case of this type in this study.
Case showing bloody duct ectasia
Dynamic FS T1WI axial image : g) pre-contrast, h) 1 min. A mass-type lesion (h : arrows) and bloody duct ectasia (g : arrowheads) delineated with high-signal intensity on dynamic contrast-enhanced (DCE)-MRI pre-contrast T1-weighted imaging.

the plateau pattern on DCE-MRI, and the only case of this type in this study.   Bloody duct ectasia delineation with high-signal intensity on pre-contrast T1-weighted imaging was observed in 4（50%）patients with NE-DCIS and in 18（25%）with non-NE-DCIS ; however, no significant difference was observed between the groups.   Figure 3g and h presents a case with mass-type lesion and bloody mammary duct ectasia.   Calcification using MMG was detected in none of the patients with NE-DCIS, but in 43（60.1%）with non-NE-DCIS, revealing a significant intergroup difference（*P* = 0.002）.

Discussion

It was revealed that NE-DCIS showed that the type of lesion is significantly more frequently the mass type and that TIC in DCE-MRI shows more washout pattern than non NE-DCIS.

The incidence of NE-DCIS in the present study of 10.1% was marginally higher than previously reported at 6.8% of all DCIS cases[1], as was the mean age of patients with NE-DCIS（57.3 years）compared to 50.4 years[1].   In addition, a palpable mass is rarely encountered with DCIS, and the primary complaint of many patients is bloody discharge from the nipple[1-4].   We did not examine the presence or absence of these symptoms in our patients ; however, the rate of bloody duct ectasia delineation on MRI was 50% for patients with NE-DCIS and 25% for those with non-NE-DCIS（not significant）, and delineation was found to be more common in NE-DCIS than in non-NE-DCIS.   In one study, the imaging findings for NE-DCIS were characterized by dilated mammary ducts and segmental contrast enhancement on MRI[5].

According to consensus MRI findings for DCIS, the most common lesion is a non-mass-type （59% of patients）, followed by mass-type（14%）, and focus-type（12%）[7].   In our study, non-mass-type lesions were most common in patients with non-NE-DCIS（76.1%）, and mass-type lesions accounted for only 16.9%.   In patients with NE-DCIS, mass-type lesions were most common at 87.5%, with a significant difference observed between patients with NE-DCSI and those with non-NE-DCIS.   Furthermore, intense segmental contrast enhancement was observed in 1 of 9（11%）NE-DCIS lesions and in 33 of 71（46.5%）non-NE-DCIS lesions in the present study, indicating significantly lower contrast enhancement in NE-DCIS compared with non-NE-DCIS ; these results differed from the NE-DCIS findings reported by Kawasaki *et al*[5].

On DCE-MRI, TIC was previously reported to show a plateau pattern more frequently than a washout pattern for DCIS[8]; however, we observed the washout pattern in 38.0% of our patients with non-NE-DCIS, a persistent pattern in 33.8%, and plateau pattern in 28.2%, with no significant intergroup differences in the contrast pattern.   On the other hand, for patients with NE-DCIS, the washout pattern was observed in the majority（87.5%）of patients, with a significant intergroup difference.

Calcification on MMG is reportedly rare in patients with NE-DCIS[1, 7, 9], and our cohort showed the same trend, with no calcification observed in any patient with NE-DCIS by MMG.   In contrast, calcification was observed in 43（60.1%）patients with non-NE-DCIS, thus there was a significant difference in the rendering rate of calcification between NE-DCIS and non-NE-DCIS cases.   Although we did not analyze the ultrasound findings, hypoechoic lesions with a

relatively distinct border are often found in NE-DCIS, with images characteristic of duct ectasia and lesions showing abundant blood flow on color Doppler imaging[1, 5, 7, 9]. In this study, mass-type lesions and TIC washout pattern were significantly more common in patients with NE-DCIS than in those with non-NE-DCIS on MRI and DCE-MRI, respectively. In addition, although no significant differences were observed in the rate of bloody mammary duct ectasia, it was more common in patients with NE-DCIS than in those with non-NE-DCIS. Finally, calcification was observed on MMG in 60.1% of non-NE-DCIS cases, with none found in NE-DCIS cases, thus indicating a significant between-group difference.

NE-DCIS is a relatively rare disease and a new disease concept, and thus the recommendations for therapy, prognosis, and pathology have not yet been sufficiently elucidated. Nevertheless, we believe it will become more clinically significant to differentiate between NE-DCIS and non-NE-DCIS, and that more cases must be accumulated in the future to establish guidelines for the prognosis and treatment of pateints with NE-DCIS.

Conflict of interest

There are no conflicts of interest to declare in association with this study.

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