Original article

The prevalence of lobular carcinoma in situ and its variants of breast cancer in Maharaj Nakorn Chiang Mai Hospital over a 5-year period

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Abstract

Objectives a) To study the prevalence of Lobular carcinoma in situ (LCIS) breast cancer and its variants, b) to evaluate the E-cadherin immunohistochemical staining patterns of LCIS and ductal carcinoma in situ (DCIS) and c) to evaluate the type of LCIS and co-existing invasive components.

Methods This was a retrospective review of H&E and E-cadherin stained slides in cases diagnosed LCIS between 2006 and 2010. The results were recorded and analyzed.

Results From 1,385 cases of breast cancer, 176 contained in situ components of which 19 (10.8%) were LCIS, with 16 (84.2%) of them being classical LCIS (CLCIS) and 3 (15.8%) pleomorphic LCIS (PLCIS). E-cadherin expression between LCIS and DCIS were different. Seven cases (43.8%) of 16 CLCIS revealed no expression, while 5 (31.3%) revealed focal expression and 4 (25.0%) focal positive loss of expression. Of 163 DCIS cases, 126 (77.4%) demonstrated strong expression, whereas 21.5% and 1.2% revealed faint and focal loss of expression, respectively. All 19 (100%) LCIS cases were coexisting with invasive carcinoma.

Conclusions There is still a need to distinguish between LCIS and DCIS. Awareness of a possible encounter of a non-classical type LCIS during daily practice is important, due to different management. E-cadherin immunohistochemical staining is useful for confirming the diagnosis of LCIS. Clinical follow-up to define the natural history and most appropriate management for CLCIS and its variants should be carried out. **Chiang Mai Medical Journal 2012;51(4):111-117.**

Keywords: Lobular neoplasm, lobular carcinoma, ductal carcinoma, E-cadherin

Introduction

Lobular carcinoma in situ (LCIS) was first characterized in 1941 as a distinct entity by Foote and Stewart [1]. Clinically, LCIS is often multicentric and frequently bilateral. Therefore, bilateral mastectomies were often performed as treatment in the past [2].

The management of lobular neoplasm (LN) is still evolving and there are no comprehen-

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sive guidelines for it. Although the distinction between PLCIS and high-grade DCIS can be difficult by histologics alone, E-cadherin immunohistochemical staining is very useful, since absence of reactivity is diagnostic for LCIS [3-5], and both CLCIS and PLCIS [2]. Thus, it is important to understand the natural history to define the most appropriate management of LCIS lesions that seem to be different among the LCIS group, and certainly between LCIS and DCIS. Only a few studies of lobular neoplasm have been carried out in Thailand [6], therefore, this study obtained more information as a starting point for further investigations.

Materials and methods

All breast cancer cases diagnosed at Maharaj Nakorn Chiang Mai Hospital, Thailand, between January 2006 and December 2010 were reviewed. Only cases diagnosed with LCIS and DCIS with or without invasive components were included in this study. All specimens (H&E stained and E-cadherin immunostained slides) were reviewed by three pathologists (BC, NS and SR), important findings were recorded (interrater reliability: 0.97).

In this study, LCIS was classified into three variants [2]; i.e. classical, pleomorphic and necrosis, in accordance with three parameters including 1) nuclear grading, 2) presence or absence of necrosis, and 3) mitotic activity.

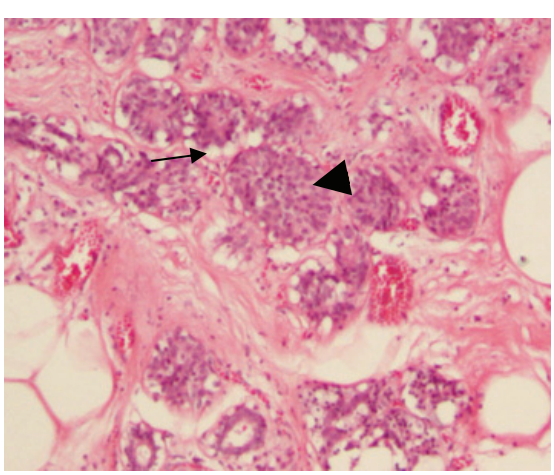

Figure 1. Classical lobular carcinoma in situ. Lobular distention containing discohesive uniform cells with rather small nuclei (arrow head), surrounded by myoepithelial cells (arrow) (H&E,100x).

CLCIS consisted of a cellular population of discohesive uniform small cells, as shown in Figure 1. In addition, CLCIS can be further categorized as type A (small-sized cells) or type B (large-sized cells) [2, 7].

PLCIS comprised a cellular population of variably discohesive pleomorphic medium to large cells that were at least 4 times the eccentric nuclei of small lymphocytes, and distinct from prominent nucleoli [8]. Necrosis and microcalcification were frequently present. In comparison to high grade DCIS, PLCIS demonstrated discohesive architecture, intracytoplasmic mucin with targetoid inclusions, and frequent presence of adjacent CLCIS [2, 8], as shown in Figure 2.

Necrosis LCIS (NLCIS) has the cytologic and architectural features of CLCIS, with prominent distention of the glandular spaces by neoplastic cells and a presence of tumor necrosis. The necrosis may be punctuated or comedo-type.

In this study, E-cadherin immunohistochemical expression patterns were classified into 5 categories; i.e. negative (no expression), positive (positive expression in all tumor cells), faint positive (weakly positive expression in all tumor cells), focal loss (positive expression in most of the tumor cells) and focally positive (positive expression in a small number of the tumor cells), as seen in Figure 3. In cases of ambiguous expression, the final diagnosis was based on H&E morphology.

Statistical analysis

SPSS for Windows, version 17 was used for statistical analysis.

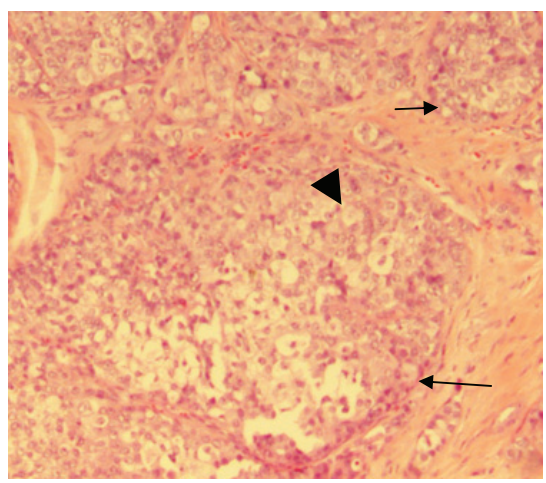

Figure 2. Pleomorphic lobular carcinoma in situ (PLCIS). The lobular distention with pleomorphic cellular clusters (arrow) of discohesive marked pleomorphic cells (arrow head) surrounded by myoepithelial cells (H&E, 400x).

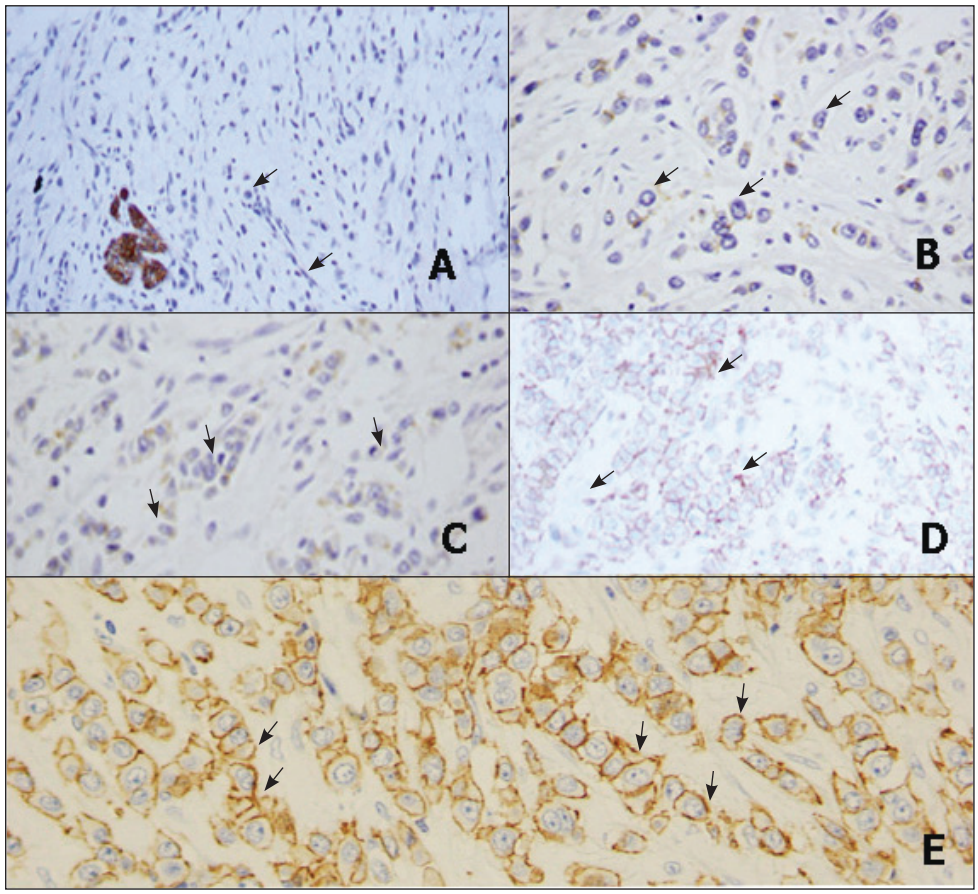

Figure 3. E-caherin immunohistochemical expression patterns.
A = Negative: no expression in all tumor cells (arrow head) [normal ductal epithelium with strong positive expression (arrow)],
B = Focal expression: positive in a small number of the tumor cells (arrow),
C = Focal loss of expression: positive in most of the tumor cells (arrow),
D = Faint expression: weakly expression in all tumor cells (arrows),
E = strong expression in all tumor cells.

Results

From 1,385 cases of breast cancer in Maharaj Nakorn Chiang Mai Hospital between January 2006 and December 2010, 176 contained in situ components, of which 19 (10.8%) were LCIS (13 pure LCIS, and 6 combined LCIS with DCIS) and 157 DCIS (89.2%). In this study, only two variants of 19 LCIS were noted; 16 (84.2%) CLCIS and 3 (15.8%) PLCIS. Regarding DCIS components, 26 (15.9 %) cases were pure comedo pattern, and 69 (42.3%) combined comedo- and non-comedo patterns, whereas 68 (41.7%) were non-comedo patterns, as shown in Table 1.

The age of patients with carcinoma in situ ranged from 28 to 78 years old, with a mean age of 52.0 years. In 92 (52.3%) of the 176 cases, carcinoma was found on the left breast, with a right to left ratio of 1:1.1.

All 19 (100%) LCIS cases were found to associate with invasive carcinoma; invasive ductal carcinoma (IDC), invasive lobular carcinoma (ILC) or combined IDC and ILC, as shown in Table 2. Of 163 DCIS cases, 43 (26.4%) were DCIS alone, whereas the remaining 120 (73.6%) were combined with LCIS, invasive ductal carci-

Table 1. Frequency of variants of DCIS and LCIS

Type	n (%)
DCIS	
Comedo	26 (15.9)
Comedo + non-comedo	69 (42.3)
Non-comedo	68 (41.7)
Total	**163.0**
LCIS	
Classical	16 (84.2)
Pleomorphic	3 (15.8)
Total	**19.0**

Table 2. Distribution of LCIS and DCIS and their co-existing invasive components

Type	n (%)
LCIS / IDC	6 (3.4)
LCIS / ILC	6 (3.4)
LCIS / IDC+ILC	1 (0.6)
LCIS + DCIS / IDC	4 (2.3)
LCIS + DCIS / ILC	0 (0.0)
LCIS + DCIS / IDC + ILC	2 (1.1)
DCIS	43 (24.4)
DCIS / IDC	109 (61.9)
DCIS / ILC	3(1.7)
DCIS / IDC + ILC	2(1.1)

Note: LCIS = Lobular carcinoma in situ, DCIS = Ductal carcinoma in situ, ILC = Invasive lobular carcinoma, IDC = Invasive ductal carcinoma

noma and/or invasive lobular carcinoma.

From this study, E-cadherin expression patterns were different between LCIS and DCIS as well as among LCIS variants, as shown in Table 3. Among the 16 CLCIS, 7 (43.8%) cases were completely negative, while focal positive expression and focal loss expression were observed in 5 (31.3%) and 4 cases (25.0%), respectively. In the 3 PLCIS, 2 (66.6%) cases revealed focal expression, while 1 (33.3%) showed focal loss of expression. None of the LCIS cases (both CLCIS and PLCIS) revealed faint positive or positive expression of E-cadherin.

In the E-cadherin expression of the DCIS group, the comedo pattern revealed a strong expression in 23 (14.7%) cases, whereas 3 (1.9%) showed a faint expression. Two cases (1.3%) of 157 DCIS had combined comedo and non-comedo patterns that demonstrated a focal loss of E-cadherin expression.

Discussion

The term "lobular carcinoma in situ" was adopted immediately by most pathologists even though no definitive evidence of its malignant nature had been demonstrated. In 1941, Foote and Stewart [1] noted the clinical significance of LCIS as being generally multifocal, with the potential of progressing to an invasive carcinoma. Subsequent studies and reviews demonstrated a high frequency of bilaterality [2].

The reported incidence of pure LCIS in biopsied specimens constitutes about 1-6% of breast cancer cases [9, 10]. However, 22-25% of those patients were reported to have intraductal or invasive carcinoma in subsequent surgical biopsies [11-12]. It was also noted that invasive ductal carcinoma was the most common type of carcinoma to develop after LCIS [13]. Interestingly, none of pure LCIS cases in this study was observed in biopsied or major breast operation specimens. All LCIS (19 cases) coexisted with either ILC or IDC invasive carcinoma at the same ratio (ILC: IDC = 1:1), while other results in the literature show a different ratio, in which IDC is more common than ILC [14].

However, in cases of combined LCIS with DCIS, the coexisting invasive component ratio between IDC and ILC is 4:1. This study also demonstrated the nature of LCIS, which is always found as a coexisting lesion with invasive carcinoma. Thus, the data in this study also support the recommendation to perform a surgical biopsy in most patients, due to the es-existing invasive carcinoma in those cases which pure LCIS is detected in a needle core biopsy specimen [15]. However, triple test assessment should be used to evaluate and determined whether further study is required.

Table 3. Distribution of E-cadherin staining patterns in each type of lesions

	E-cadherin staining				
	Negative (%)	Focal expression (%)	Focal loss of expression (%)	Faint expression	Positive expression (%)
DCIS					
Pure comedo	0	0	0	3 (1.8)	23 (14.1)
Comedo + non-comedo	0	0	2 (1.2)	5 (3.1)	62 (38.)
Non-comedo	0	0	0	27 (16.6)	41 (25.2)
Total	**0**	**0**	**2 (1.2)**	**35 (21.5)**	**126 (77.4)**
LCIS					
Classical	7 (36.8)	5 (26.3)	4 (21.1)	0	0
Pleomorphic	0	2 (10.5)	1 (5.3)	0	0
Total	**7 (36.8)**	**7 (36.8)**	**5 (26.3)**	**0**	**0**

In most cases of CLCIS, the diagnosis can be made easily by morphology from a routine histologic basis alone. However, for pleomorphic and necrotic variants, it is difficult to distinguish from high grade DCIS. Regarding PLCIS, this variant has a more aggressive phenotype than CLCIS [2, 16, 17]. Although E-cadherin staining is known to be useful for distinguishing between these two lesions, approximately 16% of lobular carcinoma has been reported as positive E-cadherin expression [17]. In this study, none of the LCIS cases (CLCIS and PLCIS) revealed faint or positive E-cadherin expression, however, focal positive and focal loss positive staining were found in approximately 50%. Almost all DCIS cases in this study showed positive or faint positive expression, except 2 cases (1.3%), which revealed focal loss expression. In cases of ambiguous expression, the diagnosis depended on H&E morphology. Regarding problematic cases, according to other studies, p120 catenin expression can be useful, as ductal carcinoma reveals negative p120 staining whese as lobular carcinoma reveals positive staining [17]. Thus, the use of both E-cadherin and p120 studies will provide more specificity in distinguishing between lobular and ductal carcinomas. At present, the p120 antibody is not available for additional study.

In conclusion, classification is still needed for LCIS and DCIS, with constant awareness of possibly encountering a non-classical type of LCIS, due to differing management. Combined E-cadherin and p120 staining are recommended for confirming the diagnosis of LCIS. Further clinical follow-up study should be carried out to define the natural history and most appropriate management for becoming heterogenous in nature.

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ความชุกของการเกิดพยาธิสภาพของมะเร็งเต้านมชนิด lobular carcinoma in situ และ variants ของโรงพยาบาลมหาราชนครเชียงใหม่ในช่วง 5 ปี

สุชานัน รัตนสาลี, พ.บ., เบญจพร ไชยวรรณ์, พ.บ., นีลยา สุคำวัง, พ.บ.
ภาควิชาพยาธิวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่

วัตถุประสงค์ เพื่อศึกษาความชุกการเกิดพยาธิสภาพของเต้านมชนิด lobular carcinoma in situ (LCIS) และ variants, เพื่อศึกษาความแตกต่างของ E-cadherin expression ระหว่าง lobular carcinoma in situ และ variants กับ ductal carcinoma in situ (DCIS) และเพื่อศึกษาความสัมพันธ์ ระหว่าง carcinoma in situ กับ invasive component

วิธีการศึกษา ศึกษาย้อนหลังโดยศึกษาจาก H&E slides และการย้อม E-cadherin ในช่วงระยะเวลาที่ทำการศึกษา

ผลการศึกษา ในช่วง เดือนมกราคม 2549 ถึง ธันวาคม 2553 มีผู้ป่วยมะเร็งเต้านมทั้งหมด 1,385 ราย ในโรงพยาบาลมหาราชนครเชียงใหม่ 176 ราย มีรอยโรคของ carcinoma in situ จากการศึกษาครั้งนี้ พบรอยโรค LCIS 19 ราย (ร้อยละ 10.8) แบ่งเป็นสองชนิดคือ classical LCIS (CLCIS) จำนวน 16 ราย (ร้อยละ 84.2) และ pleomorphic LCIS (PLCIS) จำนวน 3 ราย (ร้อยละ 15.8) และพบว่ารอยโรค LCIS ทั้งหมด 19 (ร้อยละ 100) ราย พบร่วมกับมะเร็งระยะลุกลามชนิด invasive ductal carcinoma (IDC) และ/หรือ invasive lobular carcinoma (ILC) การย้อม E-cadherin ให้ผลแตกต่างกันระหว่าง CLCIS, PLCIS และ DCIS ในกลุ่ม CLCIS พบว่า 7 (ร้อยละ 36.8) ราย ไม่มีการติด E-cadherin เลย ในขณะที่พบลักษณะการติดสี แบบ focal positive expression 5 ราย (ร้อยละ 26.3) และ focal loss of expression 4 ราย (ร้อยละ 21.1) ส่วนกลุ่ม DCIS พบว่า 126 ราย (ร้อยละ 77.3) ติดสีแบบ strong expression, 35 ราย (ร้อยละ 21.5) เป็นแบบ faint expression และ 2 ราย (ร้อยละ 1.2) เป็นแบบ focal loss of expression

ผลการศึกษา การแยกรอยโรคระหว่างกลุ่ม LCIS (classical and non-classical type) และ DCIS ยังคงมีความสำคัญ เพราะมีการดำเนินโรคแตกต่างกันและมีผลต่อแนวทางในการรักษาผู้ป่วย ส่วนการแยกชนิดของ LCIS นั้น พบว่าการย้อม E-cadherin สามารถช่วยยืนยันการวินิจฉัย LCIS ได้ แต่อย่างไรก็ตามควรมีการติดตามศึกษาการดำเนินโรคของผู้ป่วย LCIS เพิ่มเติมเพื่อประโยชน์ในการดูแลรักษาผู้ป่วยอย่างเหมาะสมต่อไป **เชียงใหม่เวชสาร 2555;51(4):111-117.**

คำสำคัญ: Lobular neoplasm, lobular carcinoma, ductal carcinoma E-cadherin