Aberrant E-cadherin Expression in Lobular Carcinoma in Situ:

A comprehensive immunohistochemical evaluation of N-terminal, Extracellular, and C-terminal E-cadherin domains

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Lay Abstract

Lobular carcinoma in situ (LCIS) is considered both a marker of increased breast cancer risk as well as a lesion that itself can directly progress to invasive lobular breast cancer. The cells that make up LCIS are confined to the small breast ducts (called lobules) but they do not stick together very well the way normal cells do. This is due to the loss of expression of a molecule on the surface of the LCIS cells called E-cadherin (E-cad). We found that while most LCIS cases show total loss of expression of E-cadherin, about one third show abnormal (aberrant) expression of various parts of this molecule. Understanding why this happens could be important for further understanding the biology of LCIS and, in turn, may lead to a better understanding of what makes some cases of LCIS progress to invasive lobular carcinoma.

Background

- About 15% of invasive lobular carcinomas show aberrant expression of E-cad, but the frequency of aberrant E-cad expression in LCIS is less well characterized.
- Furthermore, among LCIS cases with aberrant E-cad expression, the domains of the E-cad molecule that are aberrantly expressed and the relationship to expression of other components of the cadherin-catenin complex and to LCIS subtype have not been previously analyzed.

Design

- Fifty cases of LCIS without concurrent invasive carcinoma diagnosed in core needle biopsies were identified and categorized, each case, as classic (type A or B), florid, or pleomorphic using the current WHO 5th edition criteria.
- In addition, for each case immunohistochemical staining was performed to identify the frequency and patterns of expression of components of the cadherin-catenin complex (Figure 1) including the E-cad N-terminal (N; 36B5, Leica), extracellular (ECD; EP700Y, Abcam), and C-terminal (C; M168, Abcam) domains, p120 catenin (EP66, Leica), and beta-catenin (17C2, Leica).
- Quantitative real-time PCR (RT-qPCR) was performed to measure mRNA expression levels of CDH1 in aberrant cases and compared to that in cases of E-cad negative LCIS and DCIS.

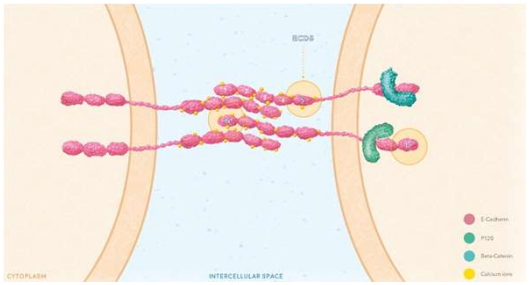


Figure 1. Cadherin-catenin complex illustration. By: Inês Canas-Marques

References

Yasui H, Kawata T, Muramatsu K, Kakuda Y, Oishi T, Norose T, Notsu A, Nishimura S, Fukuoka J, Sugino T. Expression of N-Terminal-Deficient E-Cadherin Protein in Invasive Lobular Carcinoma of the Breast. Am J Surg Pathol. 2022 Mar 1;46(3):383-391

Results

- Patients mean age at diagnosis was 55 years-old, with an age range between 38 years-old and 74 years-old.
- The most common radiologic presentation was microcalcifications, present in 36 of 50 (72%).

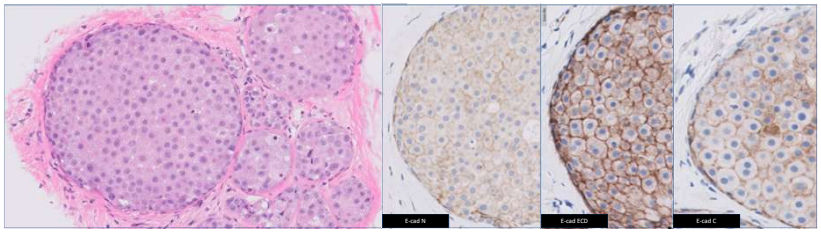


Figure 2. Pleomorphic LCIS with aberrant expression of E-cadherin domains N+ECD+C.

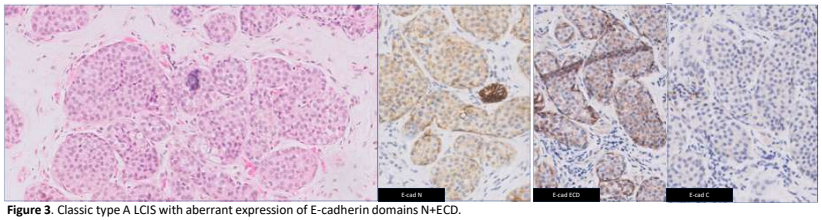


Figure 3. Classic type A LCIS with aberrant expression of E-cadherin domains N+ECD.

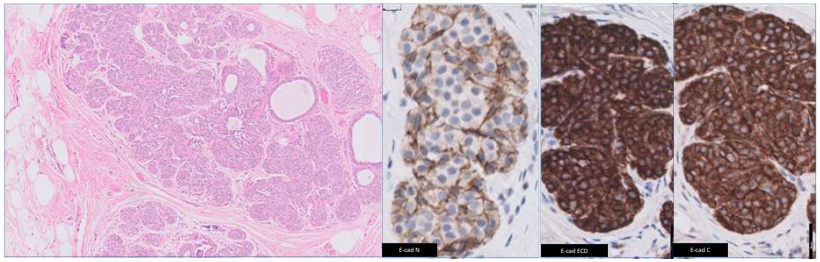


Figure 4. Classic type A LCIS with aberrant expression of E-cadherin domains C+ECD.

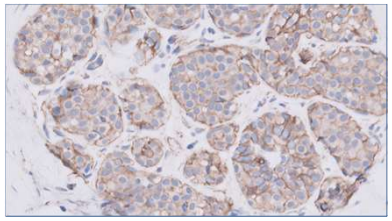


Figure 5. Classic type A LCIS with aberrant expression of p120 catenin expression.

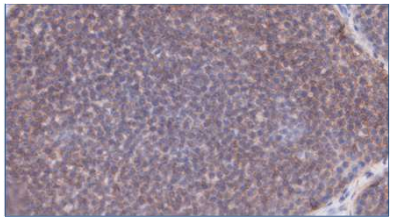
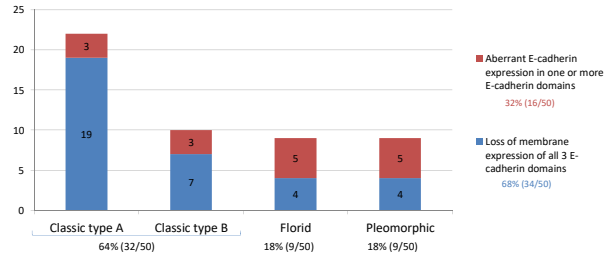


Figure 6. Classic type A LCIS with aberrant expression of beta-catenin expression.

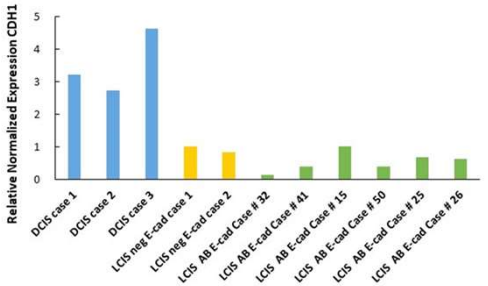


Graphic 1. Distribution of aberrant E-cadherin expression by LCIS subtype.

- Loss of membrane expression of all 3 E-cad domains was seen in 34 cases (68%), whereas aberrant expression of one or more E-cad domains was seen in 16 (32%) including 3/22 classic type A, 3/10 classic type B, 5/9 florid and 5/9 pleomorphic LCIS (Table 1).
- Aberrant E-cad expression was most often partial, fragmented membrane staining; complete, circumferential membrane staining and cytoplasmic staining were less frequently seen.
- Among the cases with aberrant E-cad expression, aberrant expression of p120 catenin (Figure 5), beta-catenin (Figure 6), or both was seen in 4 cases, 3 cases and 5 cases, respectively.

Aberrant E-cadherin	Classic A LCIS (14%,3/22)	Classic B LCIS (30%; 3/10)	Florid LCIS (56%; 5/9)	Pleomorphic LCIS (56%; 5/9)
N+ECD+C (n=5) Example: Figure 2	0	1	2	2
N+ECD (n=5) Example: Figure 3	2	0	1	2
C+ECD (n=2) Example: Figure 4	0	1	1	0
C only (n=2)	0	1	0	1
ECD only (n=1)	0	0	1	0
N only (n=1)	1	0	0	0

Table 1. Aberrant E-cadherin expression patterns in 16 of 50 cases of LCIS (32%).
Abbreviations: N, N-terminal domain; ECD, extracellular domain; C, C-terminal domain



Graphic 2. Aberrant E-cad LCIS cases had low CDH1 expression levels (mRNA) by RT-qPCR, similar to E-cadherin negative LCIS and different from DCIS cases (p=0.02).
Abbreviations: AB, Aberrant; E-cad, E-cadherin; DCIS, Ductal carcinoma in situ; LCIS, lobular carcinoma in situ

Conclusions

- ✓ To our knowledge this is the first study to evaluate aberrant E-cad expression in LCIS by examining expression of distinct domains of E-cad.
- ✓ Our results demonstrate that aberrant E-cad expression is seen in all LCIS subtypes and may be due to expression of various E-cad domains, singly and in combination.
- ✓ This, in turn, likely reflects different mechanisms of E-cad alterations in LCIS, the underlying nature of which merits further study.