

Pathology of Ductal Carcinoma *In situ* of the Breast: A Heterogeneous Entity in Need of Greater Understanding

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Abstract

Breast cancer is the commonest malignancy among Singapore women. Ductal carcinoma in situ (DCIS) is the putative precursor of the majority of invasive breast cancers, and its incidence has increased dramatically with mammographic screening. It is a heterogeneous disease—radiologically, pathologically and biologically. While the diagnosis of breast cancer in its pre-invasive phase, DCIS, allows the likelihood of cure with effective therapy, issues that surround its pathological heterogeneity are often not fully understood nor recognised. In this paper, the pathology and natural history of breast DCIS are reviewed; with emphasis on pathological classification schemes that attempt to predict recurrent disease or progression to invasive cancer. The potential role of biological markers is also evaluated. Atypical ductal hyperplasia, a lesion that is often difficult to distinguish from low grade DCIS; the significance and definition of microinvasion; and the value of fine needle aspiration cytology in DCIS are discussed. In addition, pathologic-radiologic correlations of local screen-detected cases of breast DCIS are presented. Awareness of the pathological parameters that impact on the biological behaviour of breast DCIS will enable appropriate management strategies; avoiding overtreatment in biologically indolent disease, while optimising adequate therapy for aggressive lesions.

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Key words: Architecture, Classification, Mammography, Necrosis, Nuclear grade

Introduction

Breast cancer is the commonest malignancy in Singapore women, with an age-standardised rate of 46.1 per 100,000 per year and an annual increase in incidence of 3.68%. It comprises 22.8% of all local female cancers, with an annual mortality of 13.7 per 100,000 per year.¹ Ductal carcinoma *in situ* (DCIS) is the putative precursor of the majority of invasive breast cancers,² and its incidence has dramatically risen with the advent of mammography. It accounted for 25% of all screen-detected breast cancers in the Singapore breast screening pilot project.³

DCIS is a heterogeneous disease radiologically, pathologically and biologically; and it is not always an obligate precursor of invasive disease. Some lesions remain indolent and non-progressive, while there are those that relentlessly evolve into invasive cancer if not completely removed. To prevent overtreatment of indolent disease and under-treatment of aggressive lesions, proper pathologic categorisation is essential.

Natural History of Breast DCIS

The majority of DCIS lesions originate from the terminal duct-lobular unit.⁴ The risk of developing invasive breast

cancer after biopsy-detected DCIS is reported to range from 30% to 50%, with most subsequent cancers occurring in the same breast quadrant, implying that DCIS is a true anatomic precursor.² Other supporting evidence of its principal precursor status includes its presence in about 80% of invasive cancers, their (*in situ* and invasive) shared morphological characteristics,⁵ the occurrence of abnormal molecular findings⁶ and the sometimes identical genetic abnormalities.⁷

While it is established that high grade or comedo DCIS progresses quickly to invasive disease after incomplete excision,⁸ it is important to note that incidentally discovered, non-comedo DCIS is also not entirely innocuous, with 28% of women with such lesions treated by biopsy alone developing invasive carcinoma after long-term follow-up of about 15 years.⁹ Many studies that document subsequent invasive breast cancer following a diagnosis of DCIS have an over-representation of low-grade forms.⁴

Pathological Classification of DCIS

Traditional classification of DCIS is based on architectural/morphologic patterns, with categories of cribriform, comedo, micropapillary, papillary and solid

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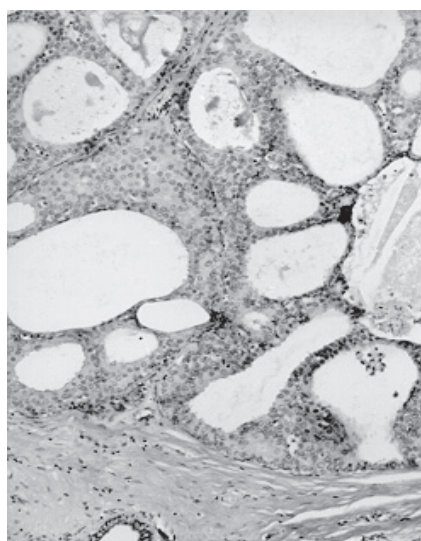


Fig. 1a.

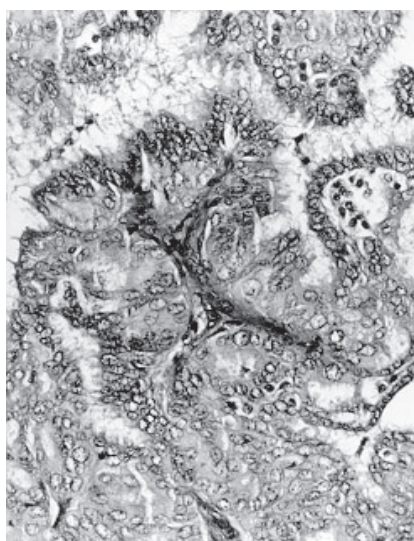


Fig. 1b.

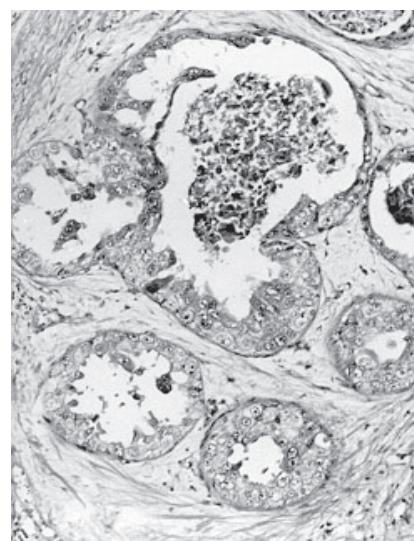


Fig. 1c.

Fig. 1. DCIS with cribriform (a), papillary (b) and comedo (c) morphologic patterns. Cribriform DCIS shows well-defined spaces rimmed by a monotonous cell population (haematoxylin & eosin, original magnification x100). Papillary DCIS consists of fronds of columnar cells with stratified nuclei, surmounting fibrovascular septa (haematoxylin & eosin, original magnification x200). Comedo DCIS reveals central luminal necrotic debris (haematoxylin & eosin, original magnification x100).

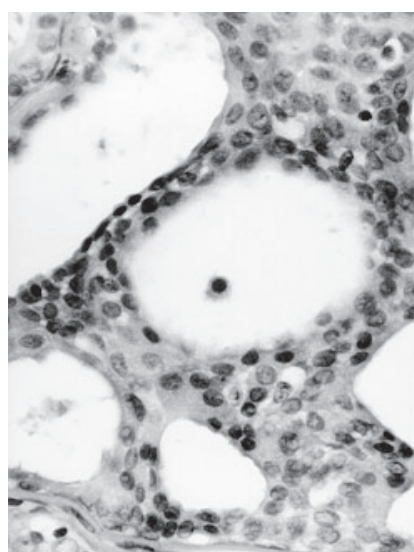


Fig. 2a.

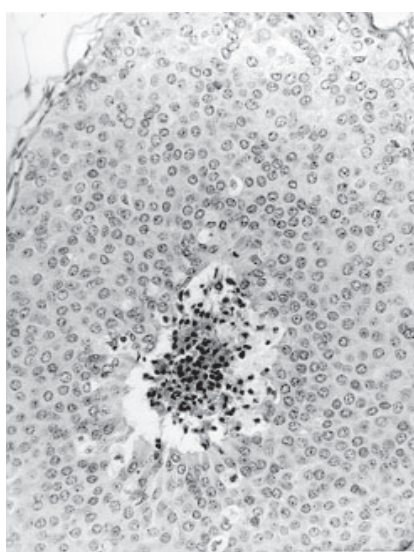


Fig. 2b.

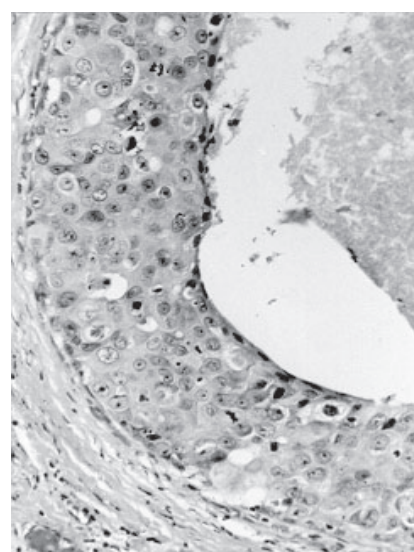


Fig. 2c.

Fig. 2. Nuclear grade stratification of DCIS into 3 tiers: (a) low nuclear grade lesion with relatively uniform nuclei (haematoxylin & eosin, original magnification x200); (b) intermediate nuclear grade DCIS with moderately enlarged, vesicular, variably sized nuclei (haematoxylin & eosin, original magnification x100); (c) high nuclear grade DCIS where the nuclei are markedly enlarged and pleomorphic, with readily discerned mitoses (haematoxylin & eosin, original magnification x200).

subtypes (Fig. 1). However, this purely architectural scheme has poor reproducibility^{10,11} and little value in predicting behaviour and recurrences,^{12,13} with the exception of the micropapillary subtype which is more likely to be multiquadrantic.⁴

New classification systems have been developed to better reflect the biologic potential of DCIS with regard to recurrence and/or progression to invasive carcinoma, with nuclear grade being an established predictor of recurrence

after local excision.^{12,14-16} The recommendations of the consensus conference committee on DCIS classification include documentation of the following histological features: nuclear grade, necrosis, polarisation and architectural pattern; and that DCIS should be stratified primarily by nuclear grade (Fig. 2).¹⁷ In a local study of image analysis on breast DCIS, it was found that quantitatively determined nuclear size and perimeter, not nuclear shape, significantly correlated with histologically-

assigned nuclear grade, validating the objectivity of classification schemes based predominantly on nuclear grade, and suggesting that nuclear grade assessment reflected visually-observed nuclear size rather than shape changes.¹⁸ Cell polarisation, synonymous with architectural differentiation, is defined as a radial orientation of cells around an intercellular luminal space.¹⁹ Other important information that ought to be incorporated in the pathology report are margin status, lesional size, presence or absence of microcalcifications, and correlation with mammographic and specimen radiography findings.¹⁷ Table I summarises the pathological parameters that are of importance in DCIS.

TABLE I: PATHOLOGIC PARAMETERS OF IMPORTANCE IN BREAST DCIS

Pathologic parameter	Comments
Nuclear grade	3 tiers: low, intermediate, high
Necrosis	Present or absent
Cell polarisation	Present or absent
Architectural pattern	Cribriform, comedo, papillary, micropapillary, solid, others
Pathologic size	Usually estimated from the number of contiguous sections containing lesional tissue; measured off the glass slide in small lesions; or determined macroscopically in large tumours
Microcalcifications	To correlate with mammographic and specimen radiology
Margins	Distance measured from lesion to radial margins

DCIS: ductal carcinoma *in situ*

Size of DCIS and Margin Assessment

The importance of size measurement in breast DCIS has often been overlooked. DCIS presenting as a large palpable mass has a significantly higher likelihood of occult invasion, local recurrence, multicentricity, axillary nodal metastasis and an overall worse prognosis than those that are discovered as small, microscopic and non-palpable lesions.² Likewise, Lagios et al²⁰ also observed that the extent of non-invasive DCIS predicted occult invasion and multicentricity. It is therefore essential that its size be addressed pathologically, and large lesions generously sampled and carefully scrutinised macroscopically in order not to overlook small solid fleshy foci of invasive disease. Though often an estimate, DCIS size can be determined from the number of contiguous sections/blocks that contain the tumour,¹⁷ if the thickness of the tissue slices is kept at a relative constant of 3 mm or it can be measured off the glass slide in small lesions. Correlation with the mammographic extent of radiologic calcifications may also be of utility in attaining a more accurate size determination.

Margin assessment is another problematic area in the pathologic evaluation of DCIS which has been treated with conservative excision. What constitutes a “clear” margin is controversial,²¹ and Silverstein et al²² have proposed a prognostic index for DCIS that incorporates margin status in its determination. While it is recommended that the distance of DCIS from the radial margins be recorded pathologically, the 3-dimensional nature of the disease makes it difficult to guarantee completeness of excision,²³ despite apparent negative margins. To require larger surgical margins may lead to high mastectomy rates.²³ More study and long-term follow-up are necessary to resolve this issue.

Biological Markers in DCIS

Interest in biological markers in breast DCIS has centred on their potential in predicting clinical behaviour.²⁴ Reported studies, however, have been mostly confined to their correlation with morphologic parameters or inter-relationship with other biological markers. Negative oestrogen receptor (ER) and progesterone receptor (PR) status, positive expression of *cerbB2* and *p53* protein and high proliferative activity have been associated with poorly-differentiated²⁴ or comedo type DCIS.²⁵⁻²⁷ Mack et al²⁸ also found lesional size and *cerbB2* positivity to be related to more aggressive clinical behaviour and advanced histologic features respectively. Close correlation between individual biomarkers like *cerbB2* and *p53* immunoexpression with high proliferative activity and negative PR,^{6,29} *cerbB2* overexpression with high S-phase fraction and proliferative index,³⁰ and loss of *bcl2* expression with immunopositivity for *p53* and *cerb2* proteins³¹ have been documented in breast DCIS.

The utility of biological markers for prognostication in DCIS, however, has so far been limited. Tamoxifen has been used to treat DCIS in randomised trials and thought to be of benefit,³² but recent work has suggested that anti-oestrogen therapy should be reserved for ER positive DCIS lesions,³³ and the evaluation of ER status may thus become of therapeutic importance in these circumstances.

Pathologic-radiologic Correlations in Screen-detected DCIS

While breast DCIS tended to present as symptomatic, clinically palpable lumps during the pre-mammographic era, mammography is now the main modality for its detection as up to 60% of DCIS lesions are associated with radiologic calcifications,³⁴ and this value is probably higher today with improved mammography techniques and resolution.

In the Singapore breast screening pilot project in which 25% (34 cases) of all cancers were DCIS,³ it was found that radiologic calcifications were detected in 94% of these cases.³⁵ Mammographic estimation of lesional size

correlated significantly with pathological size, with an enhanced degree of agreement when there was evidence of histologic necrosis. There was also a trend for crushed stone-like and casting type radiologic calcifications to be associated with DCIS of higher nuclear grade and necrosis.³⁵

With mammography being an established tool for breast cancer detection, it is essential that pathologic interpretation of lesions excised for mammographic abnormalities be made with the knowledge of what and approximately where in the submitted specimen the abnormality is. Unfortunately, it is not uncommon that the pathology laboratory receives mammographically-localised excision specimens without an accompanying specimen X-ray or the necessary information of what/where the radiologic lesion is, undermining proper pathologic interpretation. There is much to glean from appropriate pathologic-radiologic correlation, as not all histologic calcifications identified correspond to the radiologic abnormality, as demonstrated in the local study of screen-detected DCIS, in which all 34 DCIS cases contained histological micro-calcifications, with 62% of these being discovered within the adjacent benign breast tissue as well.³⁵

Atypical Ductal Hyperplasia (ADH)

ADH includes a spectrum of lesions that resemble florid epithelial hyperplasia at one end and low grade DCIS, mostly cribriform in architecture, on the other. It is a borderline lesion whose recognition is often beset with problems of inter-observer reproducibility.³⁶ As a practical guide, ADH is diagnosed when features strongly resemble but fall short of DCIS; it tends to be a small lesion, usually 2 to 3 mm in extent.

Its differentiation from DCIS is of current importance, as ADH carries an increased risk (about 4.3 times that of the general population)³⁷ of subsequent breast cancer development in either breast, while DCIS confers a risk of invasive cancer specific to the affected site.³⁸ Hence, women with ADH are followed up, while those with DCIS are subjected to definitive treatment. Nevertheless, this need for a rigid distinction may become unnecessary with emerging findings based on clonality and identification of specific genetic lesions, that suggest that some forms of breast cancer may indeed arise from lesions morphologically recognised as ADH.³⁹

Microinvasion

The definition of microinvasion in breast carcinoma has been controversial, being lumped together with “minimally invasive breast cancer”, defined as “a few high power fields” in extent⁴⁰ or arbitrarily designated as invasion not more than 2 mm from the basement membrane of the

adjacent *in situ* component.⁴¹ It has also been defined as a single focus of invasion not more than 2 mm in extent, or up to 3 foci, each measuring not more than 1 mm.⁴² Microinvasion is a lesion that is almost always associated with extensive DCIS.⁴³ The currently accepted definition as adopted by the TNM system (T1mic) clarifies it as cancer cells extending beyond the basement membrane into adjacent tissues with no focus larger than 1 mm, using only the largest focus for classification.⁴⁴ This criterion is also recommended in the United Kingdom breast screening pathology guidelines,⁴⁵ which also adds the caveat that the invasive focus should enter the interlobular stroma. It is believed that with this restrictive definition, microinvasive carcinoma has a prognosis similar to the accompanying high-grade DCIS⁴⁶ with little risk of axillary nodal metastases, and hence a management policy similar to DCIS is advocated.⁴³

Fine Needle Aspiration Cytology (FNAC) in Breast DCIS

The morphologic diversity of breast DCIS is reflected in its cytologic features, and it is still controversial as to whether FNAC can accurately distinguish DCIS from ADH on one hand and invasive carcinoma on the other. The presence of tumour cells forming tubular structures and stromal fragments are thought to be indicators of invasive carcinoma,⁴⁷ but their rare occurrence in aspirates makes the clinical utility of this finding uncertain. Other investigators have suggested that cohesive groups of atypical ductal cells associated with dispersed cells in a necrotic background; hyperplastic ductal cells with malignant cells or necrosis; or tissue fragments in cribriform patterns point to DCIS.⁴⁸ Despite these, it is generally agreed that FNAC is not a reliable method for diagnosing *in situ* versus invasive breast cancer,⁴⁹⁻⁵¹ as diagnosis of DCIS requires an assessment of architecture and basement membrane integrity, both of which need histology for proper evaluation.

Conclusion

The heterogeneity of breast DCIS makes its biology and natural history difficult to predict with certainty. Questions on the ideal and appropriate treatment of the diverse morphologic lesions grouped under the rubric of DCIS remain largely unanswered. The current role of pathology is to accurately diagnose such lesions, stratify them into categories that predict biologic behaviour, ascertain size and assiduously determine margins. Future directions would include further elucidation of the molecular genetic profile of these DCIS lesions, which can yield information beyond what can be learnt from pure morphology, and perhaps lay the foundation for optimum and effective therapy.

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QUESTIONS

1. Breast ductal carcinoma *in situ* (DCIS)
 - a) is the precursor of the majority of invasive breast cancers.
 - b) accounted for 25% of all screen-detected cancers in the Singapore breast screening project.
 - c) is an obligate precursor of invasive carcinoma.
 - d) can be detected through mammography.
2. Decide if the following statements are true or false:
 - a) Pathologic parameters of importance in DCIS include nuclear grade and lesional size.
 - b) Margin status is inconsequential in DCIS.
 - c) There is no need to correlate histologic findings in DCIS with radiology.
 - d) Large DCIS lesions have a higher likelihood of being associated with occult invasion and local recurrence.
3. Breast DCIS
 - a) originates from the terminal-duct lobular unit.
 - b) is found in association with 80% of invasive cancers.
 - c) does not share morphological characteristics with invasive cancers.
 - d) has genetic abnormalities that are different from invasive cancers.
4. Atypical ductal hyperplasia (ADH)
 - a) is a borderline lesion that is often difficult to diagnose.
 - b) does not resemble low grade DCIS.
 - c) a rigid distinction between ADH and DCIS may become unnecessary in the future.
 - d) confers an increased risk of subsequent breast cancer development in either breast.
5. Decide if the following statements are true or false:
 - a) Microinvasion is defined in the TNM system as cancer cells extending beyond the basement membrane into adjacent tissues with no focus larger than 1 mm.
 - b) If defined in a restrictive manner, DCIS lesions with microinvasion have a prognosis similar to that of DCIS.
 - c) Fine needle aspiration cytology can readily distinguish between invasive and *in situ* breast carcinoma.
 - d) Behaviour of DCIS is predictable.

ANSWER SHEET

Continuing Professional Development:
Pathology of Ductal Carcinoma *In situ* of the Breast

Question 1

- | | |
|-------------------------------|-----------------------------|
| a) True ☐ | False ☐ |
| b) True ☐ | False ☐ |
| c) True ☐ | False ☐ |
| d) True ☐ | False ☐ |

Question 2

- | | |
|-------------------------------|-----------------------------|
| a) True ☐ | False ☐ |
| b) True ☐ | False ☐ |
| c) True ☐ | False ☐ |
| d) True ☐ | False ☐ |

Question 3

- | | |
|-------------------------------|-----------------------------|
| a) True ☐ | False ☐ |
| b) True ☐ | False ☐ |
| c) True ☐ | False ☐ |
| d) True ☐ | False ☐ |

Question 4

- | | |
|-------------------------------|-----------------------------|
| a) True ☐ | False ☐ |
| b) True ☐ | False ☐ |
| c) True ☐ | False ☐ |
| d) True ☐ | False ☐ |

Question 5

- | | |
|-------------------------------|-----------------------------|
| a) True ☐ | False ☐ |
| b) True ☐ | False ☐ |
| c) True ☐ | False ☐ |
| d) True ☐ | False ☐ |

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